

Advances in

HETEROCYCLIC CHEMISTRY

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1984



Volume 35

ACADEMIC PRESS, INC.

(Harcourt Brace Jovanovich, Publishers)

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**ACADEMIC PRESS, INC.
Orlando, Florida 32887**

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

ISBN 0-12-020635-8

PRINTED IN THE UNITED STATES OF AMERICA

84 85 86 87 9 8 7 6 5 4 3 2 1

Preface

Two chapters of this volume deal with closely related tricyclic heteromatic systems. The last comprehensive review of the dibenzofurans appeared in 1951; the subject is now updated by Sargent and Stransky. Carbazoles have also not been comprehensively reviewed recently: this has been done in this volume by Joule.

The chemistry of four-membered rings containing one sulfur atom—the thietanes and their derivatives—is covered by Ried and Heinz, who update earlier surveys that appeared about 20 years ago.

The bipyridines, of considerable industrial and theoretical interest, are comprehensively reviewed for the first time by Summers.

Two chapters, dealing with *2H*- and *4H*-imidazoles by Sammes and the series editor, continue and conclude the series on nonaromatic azoles, which included contributions on *2H*- and *3H*-pyrroles (in Volume 33) and on *3H*- and *4H*-pyrazoles (in Volume 34).

Most of the chapters in this volume cover the literature up through 1982.

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Dibenzofurans

MELVYN V. SARGENT AND PETER O. STRANSKY

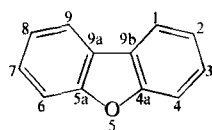
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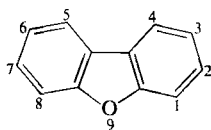
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I. Introduction

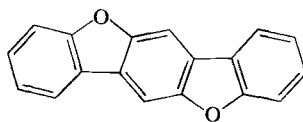
This review is concerned with the chemistry of dibenzofuran and its derivatives. Dibenzofuran is numbered as in (1) but the system shown in (2) is widespread in the older literature as is the synonym *diphenylene oxide*. The last comprehensive review on this topic was by Parham and appeared in 1951.¹ The present work covers the period up to Volume 96 of *Chemical Abstracts*, although the parts of Volume 97 received at the time of writing have been scanned. Reference to literature earlier than 1951 is made only where deemed appropriate.



(1)



(2)



(3)

The scope of the present work is limited, to some extent, by the choice and particular interest of the authors. The chemistry of reduced dibenzofurans has received attention only where it impinges on the synthesis of the fully aromatic derivatives; consequently, the chemistry of usnic acid, which

¹ W. E. Parham, *Heterocycl. Comp.* **2**, 123 (1951).

has been adequately reviewed,² is excluded. Annelated dibenzofurans such as the benzannelated dibenzofurans (brazans) and benzo[1,2-*b*:4,5-*b'*]bisbenzofuran (**3**) are excluded, although some natural products based on the latter system are mentioned. The main concerns of the present review are the synthesis of dibenzofuran and its derivatives and the reactivity of these compounds. Only the spectroscopic methods that find favor with modern practitioners of the art of structural determination are reviewed and mention is also made of such X-ray crystal structural determinations that have appeared in the literature. Theoretical aspects of the chemistry of dibenzofurans and the more mundane or abstruse spectroscopic techniques are omitted.

The main concern of the early work (before about 1955), much of which was due to Gilman, was the examination of the basic chemistry of dibenzofuran with particular reference to electrophilic substitution and metallation. A later development of dibenzofuran chemistry owed its impetus to the discovery of dibenzofuranoid lichen metabolites and the consequent synthetic efforts that this initiated.

Another development is due to the interest in polychlorodibenzofurans, spurred by their occurrence as environmental contaminants. Polychlorophenols are manufactured in large amounts (150,000 tons per annum) and find a wide range of uses. The usual method of manufacture involves the hydrolysis of chlorobenzenes, and side reactions, favored by high temperature, can lead to the production of polychlorodibenzofurans and polychlorodibenzo-*p*-dioxins.³ The Seveso incident is well known.⁴ Polychlorobiphenyls are also widely used industrial chemicals, particularly in heat exchange systems,⁵ and their pyrolysis leads to the formation of polychlorodibenzofurans.^{6,7} Polychlorodibenzofurans have also been detected in the fly ash and flue gases of incinerators and industrial heating plants. The most toxic of the polychlorodibenzofurans are 2,3,7,8-tetra-, 1,2,3,7,8-penta-, and 2,3,4,7,8-pentachlorodibenzofuran, and an extensive literature exists on the environmental pollution and the results of human exposure to these substances.⁵ A particularly tragic example of the latter occurred in 1968 in the Fukuoka prefecture of Japan after consumption of rice oil contaminated with a commercial polychlorobiphenyl.

² F. M. Dean, "Naturally Occurring Oxygen Ring Compounds." Butterworth, London, 1963.

³ C.-A. Nilsson, A. Norström, K. Andersson, and C. Rappe, *Environ. Sci. Res.* **12**, 313 (1978) [*CA* **89**, 85641 (1978)].

⁴ D. C. Edwards, *Chem. Br.* **18**, 499 (1982).

⁵ R. D. Kimbrough, ed., "Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products." Elsevier/North-Holland Biomedical Press, Amsterdam, 1980.

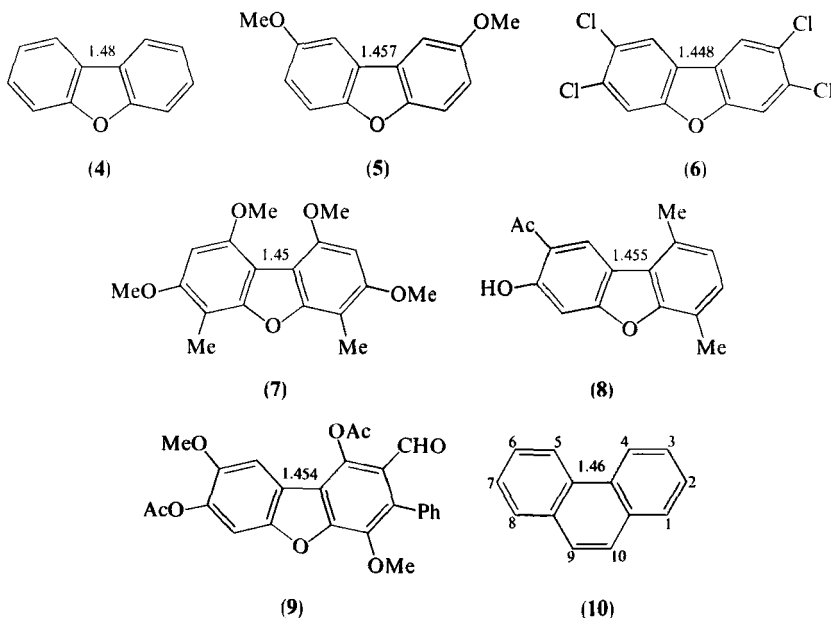
⁶ H. R. Buser and C. Rappe, *Chemosphere* **8**, 157 (1979).

⁷ G. G. Choudhry and O. Hutzinger, *Toxicol. Environ. Chem.* **5**, 67 (1982).

II. Molecular Structure and Spectroscopy

A. MOLECULAR STRUCTURE

The X-ray crystal structures of dibenzofuran (**4**),^{8,9} 2,8-dimethoxydibenzofuran (**5**),¹⁰ 2,3,7,8-tetrachlorodibenzofuran (**6**),¹¹ 1,3,7,9-tetramethoxy-4,6-dimethyldibenzofuran (**7**),¹² ruscodibenzofuran (**8**),¹³ and penioflavin diacetate (**9**)¹⁴ have been determined. These molecules, as expected, are closely planar. The bond between the two benzenoid rings in dibenzofuran (**4**) is abnormally long,⁹ and may be compared with the similar bond in phenanthrene (1.46 Å). In the case of phenanthrene (**10**), the distance between the "bay region" hydrogens at the 4- and 5-positions is 2.04 Å, which is shorter than the van der Waals separation by 0.36 Å. By contrast, the distance between the hydrogens at the 1- and 9-positions in dibenzofuran is 0.2 Å greater than the van der Waals separation, so that there is no overcrowding. The reason why the 9a–9b bond length in the substituted dibenzofurans (**5**–**9**) is shorter than the same bond in dibenzofuran (**4**) is obscure.



⁸ O. Dideberg, L. Dupont, and J. M. André, *Acta Crystallogr., Sect. B* **B28**, 1002 (1972).

⁹ A. Banerjee, *Acta Crystallogr., Sect. B* **B29**, 2070 (1973).

¹⁰ J. E. Berg, B. Karlsson, A.-M. Pilotti, and A.-C. Söderholm, *Acta Crystallogr., Sect. B* **B34**, 2041 (1978).

¹¹ C. R. Hubbard, A. D. Mighell, and I. H. Pomeranz, *Acta Crystallogr., Sect. B* **B34**, 2381 (1978).

B. NMR SPECTRA

1. ^1H -NMR Spectra

The ^1H -NMR spectrum of dibenzofuran, determined in carbon tetrachloride solution, has been analyzed as an ABCD spin system.¹⁵ The chemical shifts and coupling constants are given in Table I. Double resonance experiments showed that the two protons affording the low-field doublet and the high-field triplet, each with additional meta and para couplings, were in an ortho relationship. Without further information the low-field signal could not be assigned unequivocally to H-1 or H-4; the former assignment was preferred by analogy with the spectrum of carbazole.¹⁵ This assignment has been confirmed by examination of the ^1H -NMR spectrum of 3-deuteriodibenzofuran.¹⁶ The distance between H-1 and H-9 is longer than the distance between H-4 and H-5 in phenanthrene so that the van der Waals effect on the chemical shift is relatively small (cf. $\delta_{\text{H}4}$ for phenanthrene 8.93).

Steric interaction between the 1- and 9-positions in dibenzofurans has, however, been observed by NMR techniques. Thus saturation of the signal for the 1-methyl group in the ^1H -NMR spectrum of 1,2,3,4-tetramethyldibenzofuran (**II**) produced a 38% nuclear Overhauser effect at the 9-H.¹⁷ This may be compared qualitatively with the 33% nuclear Overhauser effect produced on the 5-H in the spectrum of 1,2,3,4-tetramethylphenanthrene by

TABLE I
CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS
(Hz) FOR DIBENZOFURAN

Proton	δ	Hz
1	7.84 ₅	$J_{12}7.6_3, J_{13}1.3_1, J_{14}0.6_1$
2	7.23 ₅	$J_{23}7.3_3, J_{24}0.8_5$
3	7.35 ₄	$J_{34}8.4_8$
4	7.48 ₃	—

¹² M. V. Sargent, P. O. Stransky, V. A. Patrick, and A. H. White, *JCS Perkin I*, 231 (1983).

¹³ M. A. ElSohly, D. J. Slatkin, J. E. Knapp, N. J. Doorenbos, M. W. Quimby, P. L. Schiff, E. M. Gopalakrishna, and W. H. Watson, *Tetrahedron* **33**, 1711 (1977).

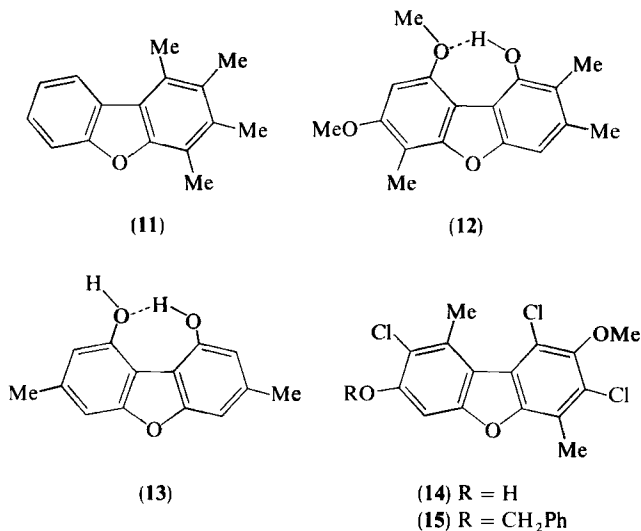
¹⁴ L. Hiltunen, L. Niinitso, T. Pakkanen, and T. Pakkanen, *Cryst. Struct. Commun.* **7**, 643 (1978).

¹⁵ P. J. Black and M. L. Heffernan, *Aust. J. Chem.* **18**, 353 (1965).

¹⁶ S. Florea, W. Kimpenhaus, and V. Farcasan, *Org. Magn. Reson.* **9**, 133 (1977).

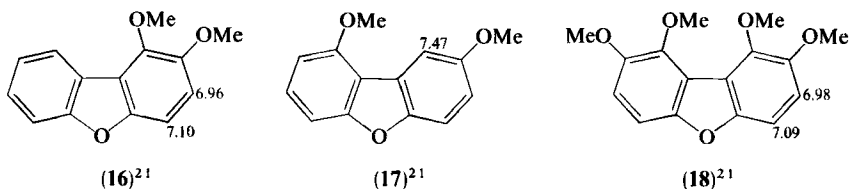
¹⁷ T. Keumi, Y. Oshima, and T. Nokura, *Bull. Chem. Soc. Jpn.* **48**, 1065 (1975).

saturation of the 4-methyl signal.¹⁸ In the spectrum of the dibenzofuranol **12**¹² the signal for the hydroxy proton is very sharp and occurs at δ 8.44, indicative of a weak hydrogen bond to the 9-OMe. A similar intramolecular hydrogen bond has been detected in 3,7-dimethyl-1,9-dibenzofurandiol (**13**) by examination of the OH stretching frequencies in its IR spectrum.¹⁹



The nuclear Overhauser method has been used to demonstrate that in the dibenzofuranol **14** the position ortho to the hydroxy group is vacant.²⁰ Saturation of the signal due to the benzylic protons of the benzyl group in the spectrum of the benzyl ether **15** gave a 39% nuclear Overhauser effect at the aromatic proton.

The chemical shift values of a number of methoxydibenzofurans are shown in formulas **16**–**28**. Assignments for the methyl group signals in the spectra

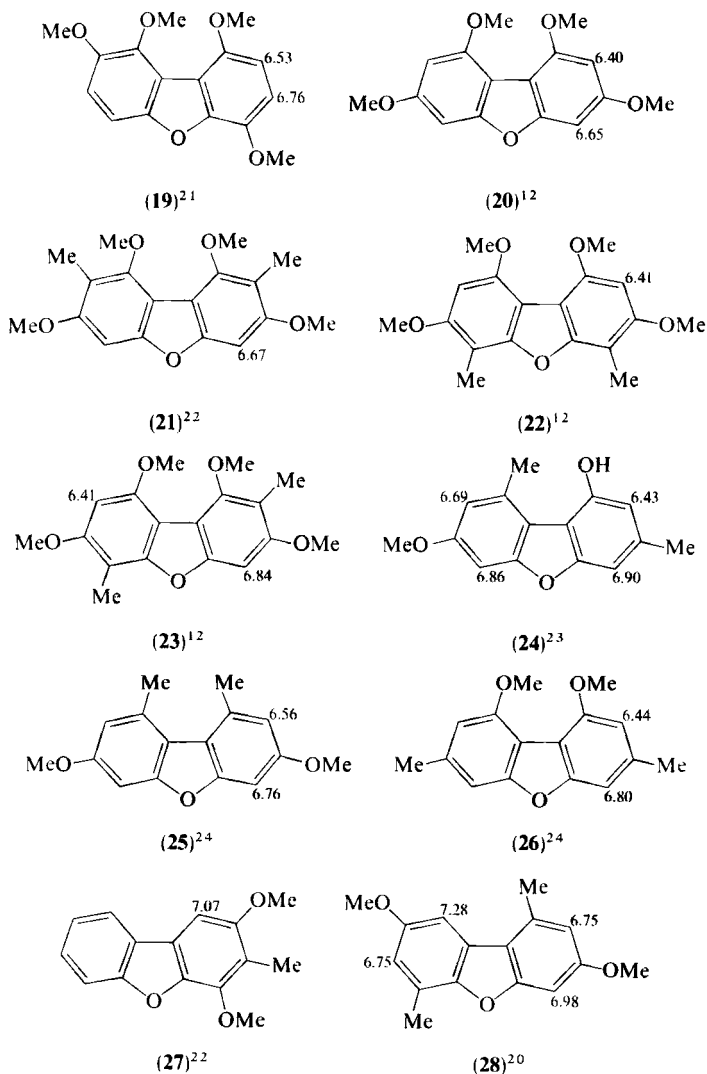


¹⁸ R. H. Martin and J. C. Noulis, *Tetrahedron Lett.*, 2727 (1968).

¹⁹ H. Musso and S. von Grunelius, *Chem. Ber.* **92**, 3107 (1959).

²⁰ T. Sala and M. V. Sargent, *JCS Perkin I*, 870 (1981).

²¹ S. Forsen and N. E. Stjernström, *Ark. Kemi* **21**, 65 (1963).



of methyl dibenzofurans have been made.¹⁷ The ^1H -NMR spectra of chloro-dibenzofurans have been reported.^{25,26}

²² C. F. Carvalho and M. V. Sargent, unpublished results.

²³ M. V. Sargent and P. O. Stransky, *JCS Perkin I*, 2373 (1982).

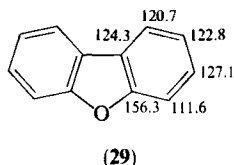
²⁴ M. V. Sargent and P. O. Stransky, *JCS Perkin I*, 1605 (1982).

²⁵ A. P. Gray, V. M. Dipinto, and I. J. Solomon, *J. Org. Chem.* **41**, 2428 (1976).

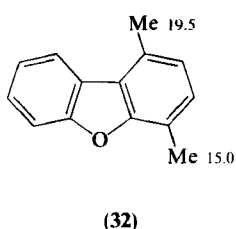
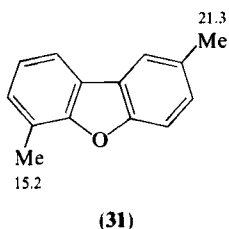
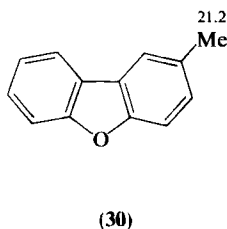
²⁶ A. Norström, S. K. Chaudhary, P. W. Albroy, and J. D. McKinney, *Chemosphere* **8**, 331 (1979).

2. ^{13}C -NMR Spectra

Assignments for dibenzofuran^{16,27-29} and a number of simple derivatives (2-bromo-,²⁸ 2,8-dibromo-,²⁸ 3-amino-,¹⁶ 3-nitro-,¹⁶ and 4-deuteriodibenzofuran,²⁹ and several alkyldibenzofurans²⁷) have been made. The assignments for dibenzofuran are shown in formula 29. The quaternary resonances for C-4a and C-9b were easily recognized because of their characteristic reduced intensity. Their assignment was made by analogy to the spectra of furans and benzofuran, and the assignment of C-9b was confirmed by off-resonance decoupling. The highest field signal belongs to C-4, shielded because of its position β to oxygen, and the assignment has been confirmed by examination of the spectrum of 4-deuteriodibenzofuran.²⁹ The assignments for the remaining carbons were made by means of single frequency off-resonance decoupling experiments²⁸ and by examination of substituent chemical shift perturbations in simple bromo²⁸ and methyl²⁷ derivatives of dibenzofuran. The $^1J(\text{CH})$ coupling constants lie between 160 and 164 Hz, and the $^3J(\text{CH})$ coupling constants are between 7 and 8 Hz.¹⁶



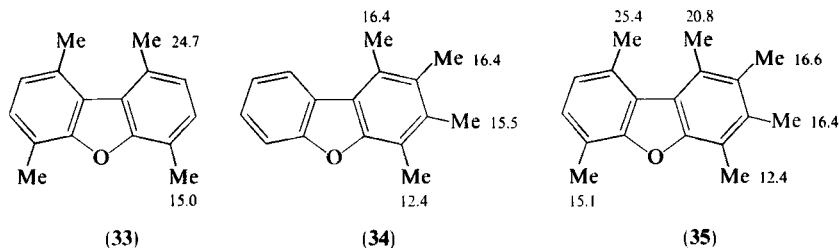
^{13}C -NMR chemical shift assignments for the methyl group resonances in the spectra of a series of polymethyldibenzofurans have been made.²⁷ Typical examples are shown in formulas 30–35. The upfield shift of the methyl groups in compound 34 is attributed to steric crowding. The marked downfield shift of the C-1 methyl group on going from compound 34 to compound 35 is attributed to twisting of the molecular plane.



²⁷ K.-P. Zeller and S. Berger, *JCS Perkin II*, 54 (1977).

²⁸ T. N. Huckerby, *J. Mol. Struct.* **54**, 95 (1979).

²⁹ J. Giraud and C. Marzin, *Org. Magn. Reson.* **12**, 647 (1979).



3. ^{17}O -NMR Spectra

The ^{17}O -NMR chemical shift (downfield from water) for dibenzofuran is 158.0 ppm. By comparison, diphenyl ether and furan exhibit the values 101.5 and 228.5 ppm.³⁰ A double bond in the α,β position relative to the oxygen atom is observed to produce a large downfield shift compared with saturated analogs probably because of the electronic charge decrease at oxygen produced by resonance. The extent of the shift may be a measure of the participation of the oxygen lone pair in resonance.

C. MASS SPECTRA

The predominant feature in the mass spectrum of dibenzofuran is the stability of the molecular ion.^{31,32} The only important fragmentation route is loss of carbon monoxide, followed by loss of a hydrogen atom, to give ion **36** at m/z 139. These decompositions give the appropriate metastable peaks.³³ In 2- and 3-methoxydibenzofuran the main fragmentation route is loss of a methyl radical from the molecular ion, followed by loss of two carbon monoxide molecules. By using ^{18}O labeling, it was found that the first loss of carbon monoxide involves only the methoxy oxygen^{31,32} 2- and 3-Dibenzofuranol undergo fragmentation by loss of carbon monoxide and a hydrogen atom. The carbon monoxide is derived predominantly from the hydroxy group but about 20% comes from the ring oxygen, as shown by ^{18}O labeling. In the case of *O*-methylnuscodibenzofuran (**37**) and its synthetic isomer (**38**),¹³ the molecular ions are again prominent and the major fragmentation pathway, as evidenced by the appropriate metastable peaks, is the successive loss of two methyl radicals. The mass spectra of a

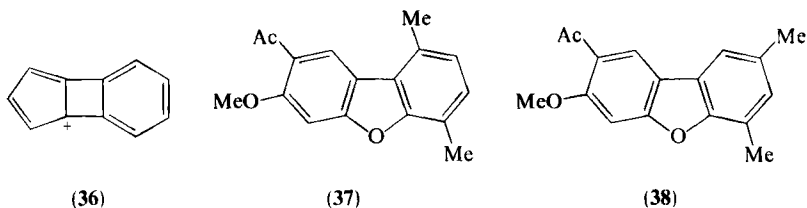
³⁰ J.-P. Kintzinger, C. Delseth, and T. T.-T. Nguyen, *Tetrahedron* **36**, 3431 (1980).

³¹ B. G. Pring and N. E. Stjernström, *Acta Chem. Scand.* **22**, 549 (1968).

³² B. G. Pring, *Chem. Commun., Univ. Stockholm*, **14** (1973) [*CA* **81**, 48892 (1974)].

³³ C. S. Barnes and J. L. Occolowitz, *Aust. J. Chem.* **17**, 975 (1964).

number of methyl dibenzofurancarboxylates have been studied.³⁴ They are typical of the methyl esters of aromatic acids with major fissions occurring by loss of methoxy and methyoxycarbonyl groups. No fragmentation of the heterocycle occurs until the ester groups are ejected in keeping with the stability of dibenzofuran to electron bombardment.



The mass spectra of a number of polychlorodibenzofurans have been examined.^{25,26} The molecular ions are invariably the base peaks and the most significant loss is that of COCl. The mass spectra of methoxy-substituted 2,8-dichlorodibenzofurans³⁵ have prominent molecular ions and, like the parent methoxydibenzofurans, their fragmentation involves the loss of a methyl radical followed by loss of carbon monoxide.

GC-MS, usually using the mass fragmentography technique (specific mass detection), is important in the analysis of mixtures containing polychlorodibenzofurans.^{36,37}

III. Synthesis of Dibenzofurans

A. FROM DIPHENYL ETHERS

1. Reaction of Diphenyl Ethers with Palladium Acetate

Diphenyl ether undergoes cyclization to dibenzofuran in good yield on treatment with 1–2 mol equiv of palladium(II) acetate in boiling solvents such as acetic acid or trifluoroacetic acid or mixtures of acetic acid and methanesulfonic acid (15:1).^{38,39} The rate of reaction is greater in the more acidic solvents, and this evidence has been taken as indicating that electrophilic attack by some palladium species is involved in the rate-limiting step;

³⁴ W. J. Davidson and J. A. Elix, *Aust. J. Chem.* **23**, 2119 (1970).

³⁵ M. T. M. Tulp and O. Hutzinger, *Biomed. Mass Spectrom.* **5**, 224 (1978).

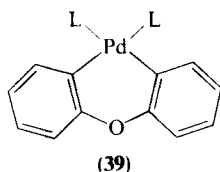
³⁶ H. R. Buser, H.-P. Bosshardt, C. Rappe, and R. Lindahl, *Chemosphere* **7**, 419 (1978).

³⁷ H. R. Buser, C. Rappe, and A. Gara, *Chemosphere* **7**, 439 (1978).

³⁸ B. Akermarck, L. Eberson, E. Jonsson, and E. Petterson, *J. Org. Chem.* **40**, 1365 (1975).

³⁹ B. Akermarck, L. Eberson, E. Jonsson, and E. Petterson, *Ger. Offen.* 2,418,503 [*CA* **84**, 30929 (1976)].

an intermediate of the type **39** is suggested.³⁸ Bis(4-methylphenyl) ether undergoes cyclization with catalytic amounts of palladium(II) acetate and acetylacetone in ethylene glycol diacetate at 150°C under a 50-Kg cm⁻² pressure of oxygen and nitrogen (1:1), but the yield of 2,8-dimethyldibenzofuran is only 29% based on the 58% of starting material consumed after 5 h; dimers (10%) of the diphenyl ether are also formed.⁴⁰ Under these conditions 3-methylphenyl 4-methylphenyl ether undergoes cyclization to 2,7-dimethyldibenzofuran rather than to the more hindered 1,8-dimethyldibenzofuran, and 4-nitrophenyl phenyl ether affords 2-nitrodibenzofuran, both in low yield.



The acid-catalyzed reaction (see Table II) has been applied to a range of substituted diphenyl ethers, particularly chlorinated compounds.^{26,41,42} In general, where more than one mode of cyclization is possible, the less sterically hindered product results. Longer reaction times and larger amounts of palladium(II) acetate are required to produce acceptable yields of the more highly substituted dibenzofurans.

TABLE II
CYCLIZATION OF DIPHENYL ETHERS TO DIBENZOFURANS WITH
PALLADIUM ACETATE UNDER ACIDIC CONDITIONS

Diphenyl Ether	Dibenzofuran	Yield (%)	References
3,3'-Cl ₂	3,7-Cl ₂	47	26
3,3',4-Cl ₃	2,3,8-Cl ₃	46	26
3,3',4,4'-Cl ₄	2,3,7,8-Cl ₄	43	26
2,2',4,4',5,5'-Cl ₆	1,2,4,6,8,9-Cl ₆	36	26
2,2',3,3',4,4'-Cl ₆	2,3,4,6,7,8-Cl ₆	55	26
3-OMe-5-Me	3-OMe-1-Me	23	24
	1-OMe-3-Me	26	—
3,5-(OMe) ₂	1,3-(OMe) ₂	53	24
3,3'-(OMe) ₂	3,7-(OMe) ₂	34	24
2-CO ₂ Me-5-OMe-3-Me	4-CO ₂ Me-1-OMe-3-Me	35	24
3,3',5,5'-(OMe) ₄ -2,4'-(Me) ₂	1,3,7,9-(OMe) ₄ -2,6-(Me) ₂	10	24

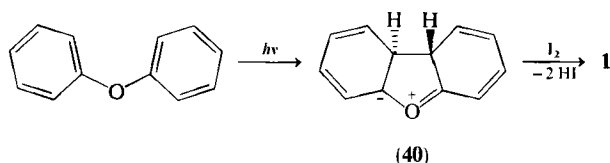
⁴⁰ A. Shiotani and H. Itatani, *JCS Perkin I*, 1236 (1976).

⁴¹ A. Norström, K. Andersson, and C. Rappe, *Chemosphere* **5**, 419 (1976).

⁴² A. Gara, C.-A. Nilsson, K. Andersson, and C. Rappe, *Chemosphere* **8**, 405 (1979).

2. Photochemical Ring Closure of Diphenyl Ethers

Diphenyl ether undergoes cleavage on ultraviolet irradiation in alcoholic solvents,^{43,44} but irradiation of dilute solutions in cyclohexane in the presence of an equimolar amount of iodine as oxidant produces dibenzofuran^{27,45} As in heteroatom-directed photoarylations,⁴⁶ a conrotatory electrocyclization producing the carbonyl ylide intermediate **40** (Scheme 1) is



SCHEME 1

probably involved, and the intermediate then undergoes oxidation by iodine, producing dibenzofuran. In keeping with this mechanism, the kinetic isotope effect for the cyclization of 2-deuteriodiphenyl ether is 1.12 ± 0.05 .⁴⁷ The cyclization reaction is scavenged by *trans*-1,3-pentadiene, suggesting that the reactive species of diphenyl ether is in a triplet state.⁴⁷

This reaction has been used to synthesize a range of alkyl dibenzofurans (Table III), but it fails when the expected product will be subject to the

TABLE III
SYNTHESIS OF ALKYLDIBENZOFURANS BY PHOTOCYCLIZATION
OF DIPHENYL ETHERS^{27,45}

Dibenzofuran	Yield (%)	Dibenzofuran	Yield (%)
Dibenzofuran	55	1,2,3,4,6,9-(Me) ₆	40
2,8-(Me) ₂	45	1,2,3,4,6,7,9-(Me) ₇	36
4,6-(Me) ₂	45	1,2,3,4,6,7,8,9-(Me) ₈	34
2,6-(Me) ₂	45	1- <i>i</i> Pr-4-Me	25
1,4-(Me) ₂	39	1,3-(<i>t</i> -Bu) ₂	20
1,4,6,9-(Me) ₄	35	1,3-(<i>t</i> -Bu) ₂ -6,7,8,9-(Me) ₄	0
1,2,3,4-(Me) ₄	40		

⁴³ H. J. Hagemann, H. L. Louwerse, and W. J. Mijs, *Tetrahedron* **36**, 2045 (1970).

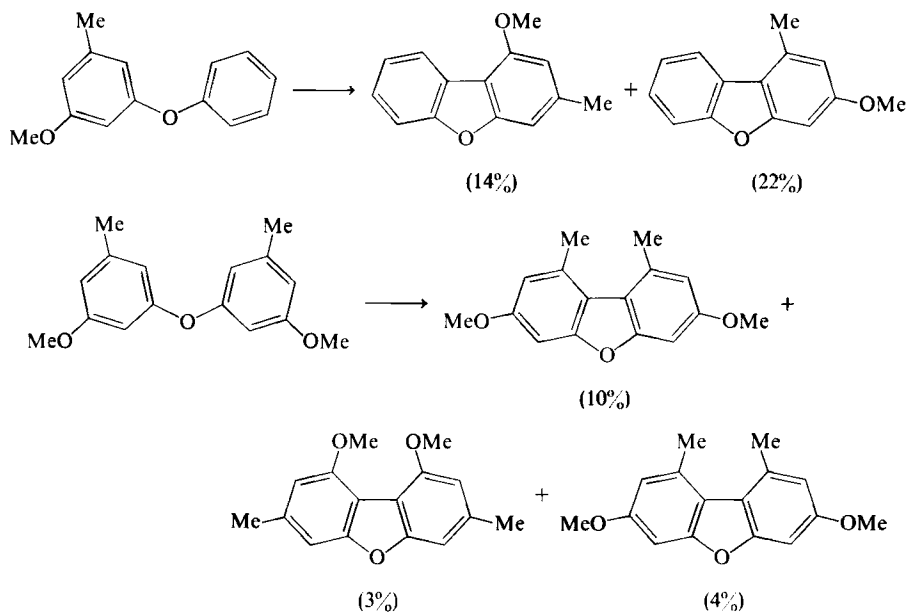
⁴⁴ Y. Ogata, K. Takagi, and I. Ishino, *Tetrahedron* **26**, 2703 (1970).

⁴⁵ K.-P. Zeller and H. Petersen, *Synthesis*, 532 (1975).

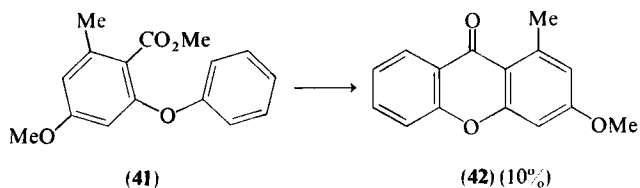
⁴⁶ A. G. Schultz, W. Y. Fu, R. D. Lucci, B. G. Kurr, K. M. Lo, and M. Boxer, *J. Am. Chem. Soc.* **100**, 2140 (1978).

⁴⁷ K.-P. Zeller and G. Gauglitz, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **32B**, 285 (1977).

severe steric hindrance of two bulky alkyl groups at the 1- and 9-positions. Where more than one mode of cyclization is possible, there appears to be little preference for a particular product (Scheme 2).²⁴ The ester **41**, in which one position of cyclization is blocked, gave no dibenzofuran, but instead the xanthone **42** was obtained (Scheme 3).²⁴

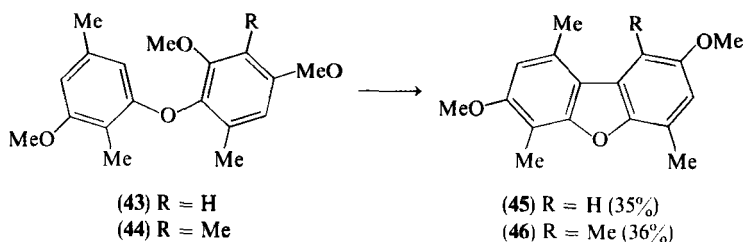


SCHEME 2

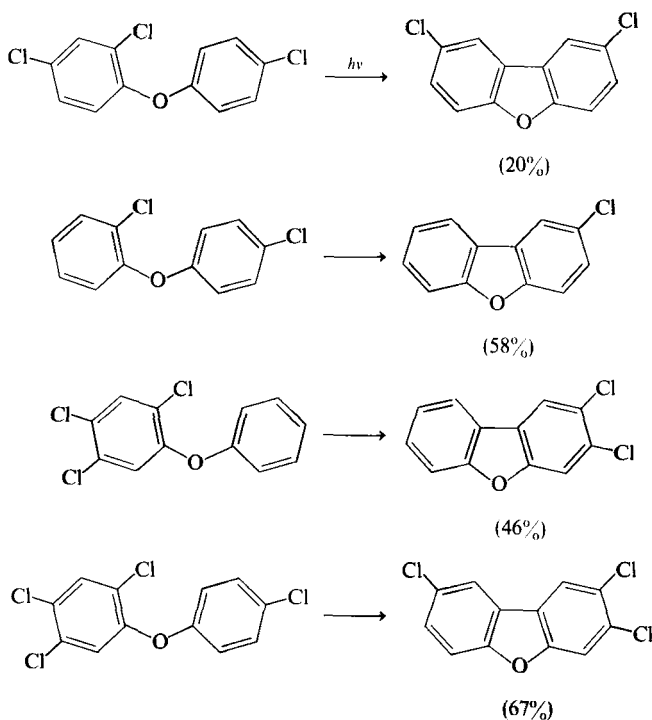


SCHEME 3

Diphenyl ethers with an ortho substituent may undergo a similar photocyclization to produce dibenzofurans by expulsion of the substituent from an intermediate 9b-substituted 9a,9b-dihydrodibenzofuran of the same type as **40**. Thus the diphenyl ethers **43** and **44** on irradiation lose methanol with the production of the dibenzofurans **45** and **46** (Scheme 4). With less highly



SCHEME 4



SCHEME 5

substituted diphenyl ethers of this type the predominant reaction was cleavage rather than cyclization.⁴⁸

Dibenzofurans also result from UV irradiation of *o*-chlorophenyl phenyl ethers,^{49,50} and better results were obtained in acetone rather than in hexane.

⁴⁸ J. A. Elix and D. P. Murphy, *Aust. J. Chem.* **28**, 1559 (1975).

⁴⁹ A. Norström, K. Andersson, and C. Rappe, *Chemosphere* **5**, 21 (1976).

⁵⁰ G. G. Choudhry, G. Sundström, F. W. M. van der Wielen, and O. Hutzinger, *Chemosphere* **6**, 327 (1977).

A number of examples are shown in Scheme 5. Where more than one mode of cyclization is possible, mixtures of products may result, and overirradiation may result in dechlorination. This method has also been used for the synthesis of chloromethoxydibenzofurans.³⁵

3. From 2-Phenoxyanilines

Synthesis from 2-phenoxyanilines is allied to the Pschorr phenanthrene synthesis, and examples are shown in Table IV. The 2-phenoxyaniline is usually diazotized in aqueous solution and then added to hot 50% sulfuric acid; the yields are invariably low, and the deaminated diphenyl ether is a common by-product. De Tar and Sagmanli⁵¹ claimed a 45% yield of dibenzofuran under these conditions, but in a later paper⁵² the maximum yield (27%) of dibenzofuran was reported as obtained from 2-phenoxybenzene diazonium tetrafluoroborate by heating the salt at 80°C with 21 *N* sulfuric acid; the yield was lower when copper powder or copper(I) chloride was added, and under these conditions diphenyl ether became a significant by-product. Irradiation of the diazonium salt from 2-phenoxyaniline produces dibenzofuran in only 1% yield and the major product (44%) is 2-phenoxyphenol.⁵³ Aprotic diazotization of simple 2-phenoxyanilines appears to offer little advantage. Treatment of 2-phenoxyaniline with *tert*-butylthionitrate in the molten state under argon gave dibenzofuran in only 5% yield,⁵⁴ and treatment of 2-(2-methoxyphenoxy)aniline with isopentyl nitrite in ethyl acetate at 50°C gave only a trace of 4-methoxydibenzofuran.⁵⁵

From limited data⁵⁶⁻⁵⁸ the generalization has been made that this method fails for the synthesis of 1-substituted dibenzofurans and for the synthesis of 4-substituted dibenzofurans unless the amino group and the potential 4-substituent are in the same ring. These generalizations are not substantiated in the synthesis of polychlorodibenzofurans. Polychloro-2-phenoxyanilines are poorly soluble and nonbasic so that the usual method is precluded. In these cases aprotic diazotization with isopentyl nitrite in tetrachloroethylene at 80°C is the method of choice. Yields, as determined by GLC, are usually of the order of 40–50%. The yields of pure isolated

⁵¹ D. F. De Tar and S. V. Sagmanli, *J. Am. Chem. Soc.* **72**, 965 (1950).

⁵² D. F. De Tar and T. E. Whitely, *J. Am. Chem. Soc.* **79**, 2498 (1957).

⁵³ R. Huisgen and W. D. Zahler, *Chem. Ber.* **96**, 747 (1963).

⁵⁴ S. Oae, K. Iida, K. Shinham, and T. Takata, *Bull. Chem. Soc. Jpn.* **54**, 2374 (1981).

⁵⁵ L. Benati, P. C. Montevocchi, A. Tundo, and G. Zanardi, *JCS Perkin I*, 1272 (1974).

⁵⁶ H. McCombie, W. G. Macmillan, and H. A. Scarborough, *J. Chem. Soc.*, 529 (1931).

⁵⁷ H. Gilman, M. W. Van Ess, and D. M. Hayes, *J. Am. Chem. Soc.* **61**, 643 (1939).

⁵⁸ W. E. Parham and R. W. Strassburg, *J. Org. Chem.* **26**, 4749 (1961).

TABLE IV
 SYNTHESIS OF DIBENZOFURANS FROM 2-PHENOXYANILINES

2-Phenoxyaniline	Dibenzofuran	Yield (%)	References
2'-CO ₂ Me-6-OMe	6-CO ₂ H-1-OMe	17	59
2',4'-(Me) ₂	2,4-(Me) ₂	8.3	58
3,5-(Me) ₂	2,4-(Me) ₂	46	58
3,5-(Me) ₂ -4-NO ₂	2,4-(Me) ₂ -3-NO ₂	37	58
3,5-(Me) ₂ -4,4'-(NO ₂) ₂	2,4-(Me) ₂ -3,8-(NO ₂) ₂	50	58
5,5'-(CO ₂ Me) ₂ -2',3'-(OMe) ₂	2,9-(CO ₂ Me) ₂ -6,7-(OMe) ₂	88	60
4,4',5-Cl ₃	2,3,8-Cl ₃	4.5	25
2',4,4',5,5'-Cl ₅	1,2,4,7,8-Cl ₅	6	25
2',3',4,5,5'-Cl ₅	1,3,4,7,8-Cl ₅	1.3	25
2',3,4,4'-Cl ₄	2,3,6,8-Cl ₄	3.7	25
3',4,5-Cl ₃	1,7,8-Cl ₃	27 ^a	25
	2,3,7-Cl ₃	14 ^a	
4-NO ₂	3-NO ₂	—	56
5-Cl	2-Cl	—	56
4'-Cl	2-Cl	—	56
4',5-Cl ₂	2,8-Cl ₂	—	56
4-Br	3-Br	—	56
5-Br	2-Br	—	56
4,4'-Br ₂	2,7-Br ₂	—	56
4',5-Br ₂	2,8-Br ₂	—	56
4'-Me	2-Me	—	61
3-CO ₂ H	Dibenzofuran	39	62
3-CO ₂ H-4'-Br	4-CO ₂ H-8-Br	11	57
5-Br-3-Me	2-Br-4-Me	44	57
5-Br-4'-OMe	2-Br-8-OMe	8	63

^a Determined by GLC.

products are much lower because of the difficulty of separation of the by-products. These are usually the deamino compound and the product derived by replacement of the amino group by a solvent-derived trichloroethenyl group. In the case of 2-(2'-chlorophenoxy)anilines, the intermediate phenyl cation attacks the neighboring ring in an ipso sense with subsequent chloride migration, and the crude product contains 5–10% of isomeric chloro-dibenzofurans.²⁵

⁵⁹ M. Tomita and H. Iwasaki, *J. Pharm. Soc. Jpn.* **75**, 1128 (1955) [*CA* **50**, 5560 (1956)].

⁶⁰ K. Freudenberg and K. C. Renner, *Chem. Ber.* **98**, 1879 (1965).

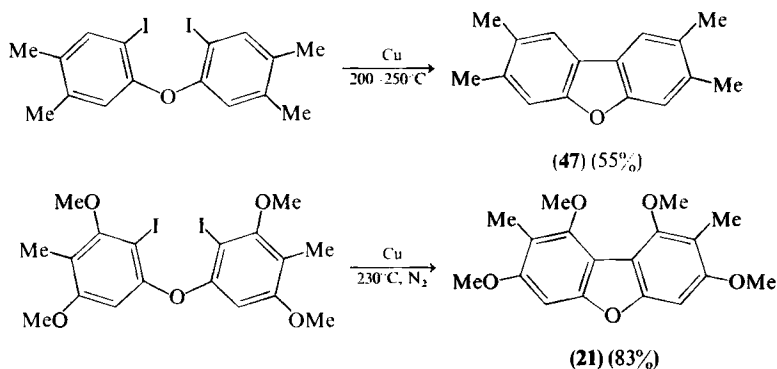
⁶¹ M. Kuroki, *Nippon Kagaku Zasshi* **89**, 527 (1968) [*CA* **70**, 3680 (1969)].

⁶² S. Natori, *Pharm. Bull.* **5**, 539 (1957) [*CA* **52**, 16326 (1958)].

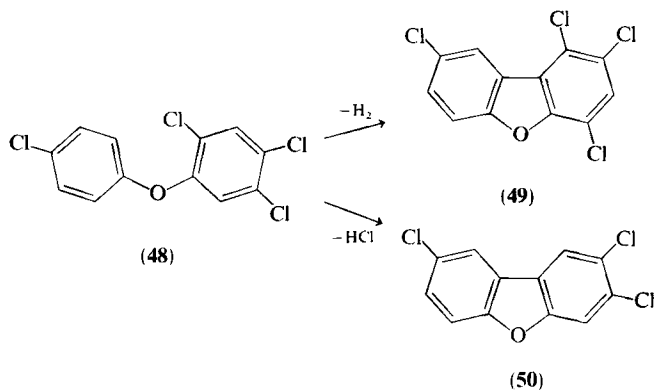
⁶³ H. Gilman and P. R. Van Ess, *J. Am. Chem. Soc.* **61**, 1365 (1939).

4. By Intramolecular Ullmann Reaction

The formation of the dibenzofuran nucleus by intramolecular Ullmann coupling of bis(2-iodophenyl) ethers has been little exploited, although the method offers potential. Mazere *et al.*⁶⁴ have obtained 2,3,7,8-tetramethyl-dibenzofuran (**47**), and Carvalho and Sargent²² have obtained the dibenzofuran **21** (Scheme 6), by this method.



SCHEME 6



SCHEME 7

It has been observed that pyrolysis of polychlorodiphenyl ethers in the presence of air at 600°C produces low yields of polychlorodibenzofurans, as well as polychlorodibenzo-*p*-dioxins, which were identified by GC-MS methods. The major reaction pathways leading to dibenzofuran formation involve loss of hydrogen and hydrogen chloride from the *o,o'*-positions.

⁶⁴ I. Mazere, I. Meirovics, V. Ozolina, and O. Neilands, *Khim. Geterotsikl. Soedin.*, 1579 (1972).

Thus 4-chlorophenyl 2,4,5-trichlorophenyl ether (**48**, Scheme 7) produced ~4% of a mixture of the dibenzofurans **49** and **50**. Only in the case of 2,3,4-trichlorophenyl 2,3,4,5,6-penta-chlorophenyl ether was production of dibenzofurans by formal loss of *o,o'*-chlorine detected. Neither product was identified, but one is presumably the expected product, 1,2,3,4,8,9-hexachloro-dibenzofuran, and the other must be due to a rearrangement.⁶⁵

Chlorination of diphenyl ether in the gas phase is unusual. At 300°C the major product is 4-chlorophenyl phenyl ether, as in the liquid phase, but as the temperature is increased (400–500°C), the amount of 4-chlorophenyl phenyl ether decreases at the expense of 3-chlorophenyl phenyl ether, and dibenzofuran is also produced.⁶⁶

B. FROM DERIVATIVES OF BIPHENYL

1. From 2,2'-Biphenyldiols

2,2'-Biphenyldiols undergo dehydration, forming dibenzofurans on treatment with a variety of acidic reagents (Table V). The usual precursors for the dibenzofurans are the 2,2'-dimethoxybiphenyls, which undergo demethylation *in situ* prior to cyclization.⁷⁰ Reagents that have been employed include boiling hydriodic or hydrobromic acids, phosphoric acid at 120°C,⁸⁴ pyridinium chloride or bromide under reflux,⁸⁶ and fusion with the

⁶⁵ R. Lindahl, C. Rappe, and H. R. Buser, *Chemosphere* **9**, 351 (1980).

⁶⁶ J. W. Engelsma and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas* **80**, 526 (1961).

⁶⁷ B. G. Pring and N. E. Stjernström, *Acta Chem. Scand.* **22**, 681 (1968).

⁶⁸ N. P. Buu-Hoi, L. Petit, and D. C. Thang, *J. Org. Chem.* **29**, 762 (1964).

⁶⁹ E. Müller, R. Mayer, B. Narr, A. Rieker, and K. Scheffler, *Justus Liebigs Ann. Chem.* **645**, 25 (1961).

⁷⁰ E. Pettersson and N. E. Stjernström, *Ark. Kemi* **21**, 49 (1963).

⁷¹ B. G. Pring and N. E. Stjernström, *Acta Chem. Scand.* **22**, 538 (1968).

⁷² H. Erdtman, F. Haglid, and N. E. Stjernström, *Acta Chem. Scand.* **15**, 1761 (1961).

⁷³ H. Musso, U. I. Zahorsky, D. Maassen, and I. Seeger, *Chem. Ber.* **96**, 1579 (1963).

⁷⁴ N. E. Stjernström, *Ark. Kemi* **21**, 57 (1963).

⁷⁵ S. Shibata, *Acta Phytochim.* **14**, 9 (1944) [*CA* **45**, 7100 (1951)].

⁷⁶ H. Musso, *Chem. Ber.* **91**, 349 (1958).

⁷⁷ C. A. Wachtmeister, *Acta Chem. Scand.* **12**, 147 (1958).

⁷⁸ D. O. Chester and J. A. Elix, *Aust. J. Chem.* **34**, 1501 (1981).

⁷⁹ C. A. Wachtmeister, *Acta Chem. Scand.* **8**, 1433 (1954).

⁸⁰ B. Akermarck, H. Erdtman, and C. A. Wachtmeister, *Acta Chem. Scand.* **13**, 1853 (1959).

⁸¹ C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc. C*, 1438 (1968).

⁸² F. R. Hewgill, B. R. Kennedy, and D. Kilpin, *J. Chem. Soc.* 2904 (1965).

⁸³ N. E. Stjernström, *Ark. Kemi* **21**, 73 (1963).

⁸⁴ F. M. Dean, A. M. Osman, and A. Robertson, *J. Chem. Soc.*, 11 (1955).

⁸⁵ N. H. Anderson, W. D. Ollis, J. G. Underwood, and R. M. Scowston, *J. Chem. Soc. C*, 2403 (1969).

⁸⁶ J.-P. Bachelet, P. Demerseman, and R. Royer, *J. Heterocycl. Chem.* **14**, 1409 (1977).

TABLE V
SYNTHESIS OF DIBENZOFURANS FROM 2,2'-BIPHENYLDIOLS AND THEIR METHYL ETHERS

Biphenyl	Dibenzofuran	Reagent	Yield (%)	References
2,2'-(OH) ₂	Dibenzofuran	HBr (180°C)	14	67
2,2'-(OMe) ₂ -5-(C ₃ H ₇)	2-(C ₃ H ₇)	Py-HCl	65	68
2,2'-(OMe) ₂ -5-Et	2-Et	Py-HCl	77	68
2,2'-(OH) ₂ -3,3',5,5'-(<i>t</i> -Bu) ₄	2,4,6,8-(<i>t</i> -Bu) ₄	350°C	74	69
2,2',3-(OH) ₃	4-OH	HBr (180°C); ZnCl ₂ (300°C)	7; 37	67; —
2,2',4-(OMe) ₃	3-OH	HBr	75	70–72
2,2',5-(OMe) ₃	2-OH	HBr	33	70, 71
2,2',6-(OMe) ₃	1-OH	HBr	—	70
2,2',4-(OMe) ₃ -3',5'-(Me) ₂	3-OH-6,8-(Me) ₂	HBr	—	13
2,2',4-(OMe) ₃ -4',6'-(Me) ₂	3-OH-7,9-(Me) ₂	HBr	—	13
2,2',4,4'-(OMe) ₄	3,7-(OH) ₂	Py-HCl; HBr	83	73; 74
2,2',4,4'-(OMe) ₄ -6,6'-(Me) ₂	3,7-(OH) ₂ -1,9-(Me) ₂	HI; HBr	45; 96	75, 76; 77
2,2',4,4'-(OH) ₄ -6,6'-(C ₅ H ₁₁) ₂	3,7-(OH) ₂ -1,9-(C ₅ H ₁₁) ₂	ZnCl ₂	74	77
2,2,4,4'-(OMe) ₄ -6,6'-(C ₅ H ₁₁) ₂	—	HBr	84	78
2,2',4,6'-(OMe) ₄	1,7-(OH) ₂	HBr	72	79
2,2',6,6'-(OMe) ₄ -4,4'-(Me) ₂	1,9-(OH) ₂ -3,7-(Me) ₂	HBr	44	80
2,2'-(OMe) ₂ -4,4'-(OH) ₂ -5,5'-(<i>t</i> -Bu) ₂	3,4-(OMe) ₂	HBr ^a	—	81
2,2'-(OH)-5,5'-(OMe) ₂ -3,3'-(<i>t</i> -Bu) ₂	2,8-(OAc) ₂	HBr ^b ; Py-HCl ^b	—; 42	82; 82
2,2',5,5'-(OMe) ₄	2,8-(OH) ₂	HBr	50	74
2,2',5,5'-(OMe) ₄ -3,3',4,4'-(Me) ₄	2,8-(OH) ₂ -3,4,6,7-(Me) ₄	HBr	—	83
2,2',3,6-(OMe) ₄	1,2-(OH) ₂	HBr	—	70
2,2',4,5-(OMe) ₄	2,3-(OH) ₂	HBr	—	70
2,2',5,5'-(OH) ₄ -4,4'-(OMe) ₂	2,8-(OH) ₂ -3,7-(OMe) ₂	H ₃ PO ₄	—	84
2,2',5,5'-(OH) ₄ -4,4'-(OMe) ₂ -6,6'-(C ₃ H ₇) ₂	2,8-(OH) ₂ -3,7-(OMe) ₂ -1,9-(C ₃ H ₇) ₂	HCl	79	84
2,2',3,3',6,6'-(OMe) ₆	1,2,6,9-(OMe) ₄ ; 1,2,8,9-(OMe) ₄	HBr ^a	—; —	21; —
2,2'-(OH) ₂ -4,4',6,6'-(OMe) ₄	1-(OH)-3,7,9-(OMe) ₄ -2,6-(Me) ₂	H ₃ PO ₄	59	85
2,2'-(OH) ₂ -4,4',6,6'-(OMe) ₄	1,3,7,9-(OMe) ₄ -2,6-(Me) ₂ ; 1,3,7,9-(OMe) ₄ -4,6-(Me) ₂	HBr ^a	20; 37	12; —
2,2',4,4',6,6'-(OMe) ₄	1,3,7,9-(OMe) ₄	HI ^a	35	12

^a Followed by methylation.

^b Followed by acetylation.

Lewis acids zinc chloride or aluminum chloride.¹ Heat alone is sometimes effective,⁶⁹ and the kinetics of the formation of dibenzofuran from 2,2'-biphenyldiol have been studied in both the presence and absence of zinc chloride. The rate and the degree of conversion are both markedly increased with increasing temperature under these conditions.⁸⁷

The major drawback to the acid-induced dehydration of 2,2'-biphenyldiols is that some functional groups are labile under the conditions of the reaction. Thus no dibenzofuran carboxylic acid has been prepared by this method.¹ *tert*-Butyl groups are also lost.^{81,82} The claim by Buu-Hoi and co-workers⁶⁸ that 3'-(2-methoxyphenyl)-4'-methoxyacetophenone undergoes smooth conversion to 2-acetyldibenzofuran on treatment with boiling pyridinium chloride has been refuted.⁸⁶ Rapid deacetylation of the former compound was found to occur in both boiling pyridinium chloride or bromide. Pyridinium chloride was ineffective for the conversion of 2,2'-biphenyldiol to dibenzofuran, but the reaction could be achieved with pyridinium bromide. When 2,2'-dimethoxybiphenyl was boiled with pyridinium bromide, the resultant dibenzofuran was accompanied by methyl dibenzofurans, the origin of which must be a Friedel-Crafts alkylation involving bromomethane.⁸⁶

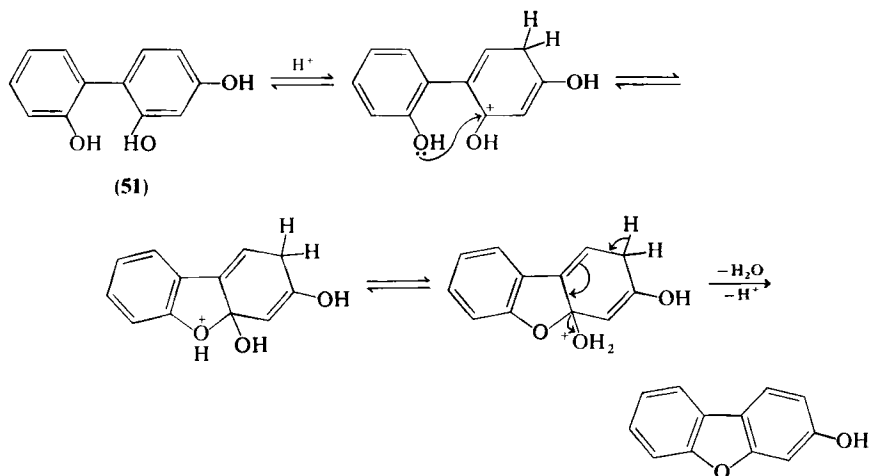
The ring closure of 2,2'-biphenyldiols and their methyl ethers has been subjected to mechanistic investigation. Pring and Stjernström⁷¹ found that the 3-dibenzofuranol resulting from cyclization of 2,2',4-trimethoxy(2'-¹⁸O)-1,1'-biphenyl had retained the label and that it was located at the ring oxygen. Similar results were obtained for the production of 2-dibenzofuranol from 2,2',5-trimethoxy(2'-¹⁸O)-1,1'-biphenyl. Hence the mechanism (Scheme 8) shown for 2,2',4-biphenyltriol (**51**), which involves the intramolecular nucleophilic attack of the 2'-hydroxy group on C-2 of the 3- or 5-protonated trisubstituted ring of the biphenyl, is indicated. The reaction is thus mechanistically similar to the acid-catalyzed formation of 2-methoxynaphthalene from 2-naphthol and methanol.^{88,89} Resorcinol and phloroglucinol also readily form methyl ethers on treatment with boiling anhydrous acidic methanol, but phenol and catechol do not. Similarly the oxygen of the hydroxy groups of hydroquinone and resorcinol undergo exchange with H₂¹⁸O at 110°C in 10 M hydrochloric acid, but for exchange with phenol and catechol a temperature of 180°C is required.^{32,90} In keeping with these considerations, ring closure of 2,2'-biphenyldiol and 2,2'-3-biphenyltriol to dibenzofuran and 4-dibenzofuranol require forcing conditions: fusion with

⁸⁷ P. D. Pistrova and G. D. Kharlampovich, *Khim. Tverd. Topl. (Moscow)*, 108 (1974) [*CA* **80**, 107565 (1974)].

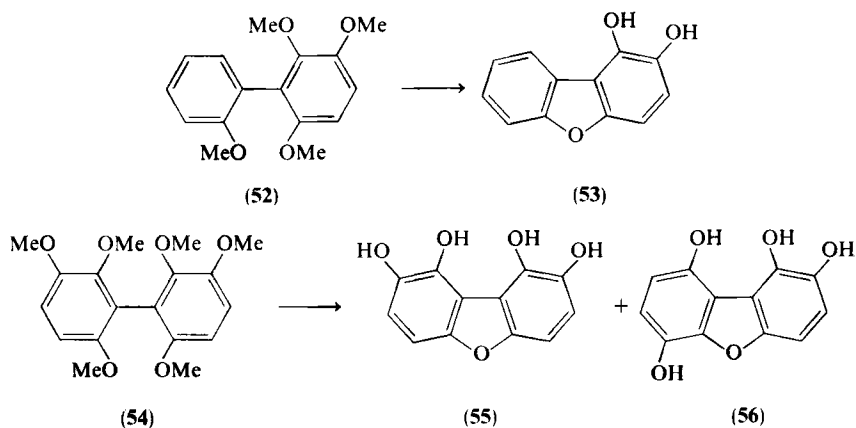
⁸⁸ K. B. Wiberg and K. A. Saegebarth, *J. Org. Chem.* **25**, 832 (1960).

⁸⁹ N. E. Stjernström, *Sven. Kem. Tidskr.* **75**, 184 (1963).

⁹⁰ S. Oae, R. Kiritani, and W. Tagaki, *Bull. Chem. Soc. Jpn.* **39**, 1961 (1966).

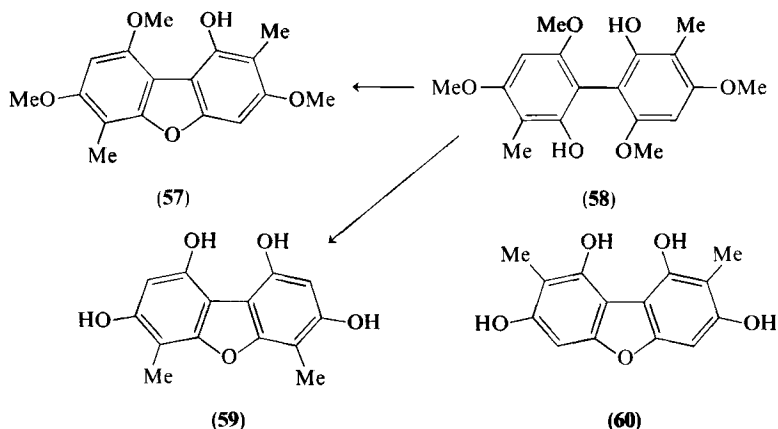


SCHEME 8



SCHEME 9

zinc chloride or treatment with hydrobromic acid at 180°C .⁶⁷ Similarly, 2,2',3,6-tetramethoxybiphenyl (52) on treatment with boiling hydrobromic acid yielded the 1,2-dibenzofurandiol 53 (Scheme 9) rather than the 1,4-diol, and the catechol portion of the molecule does not take part in the ring closure.⁷⁰ An allied example is the closure of 2,2',3,3',6,6'-hexamethoxybiphenyl (54, Scheme 9) with boiling hydrobromic acid, which furnished only the dibenzofurans 55 and 56 but no 1,4,6,9-dibenzofurantetraol.²¹ Pring³²



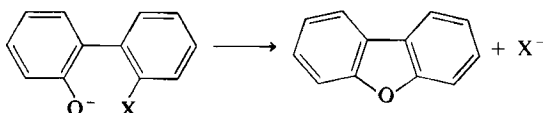
SCHEME 10

has attempted to rationalize the reluctance of *o*-dihydroxyphenyl groups to participate in acid-catalyzed aromatic nucleophilic substitution in terms of molecular orbital calculations.

Steric effects are sometimes important in determining the direction of cyclization of 2,2'-biphenyldiols. Treatment of the biphenyldiol **58** (Scheme 10) with phosphoric acid under conditions mild enough to prevent demethylation afforded the dibenzofuranol **57**⁸⁵ as expected from the operation of the mechanism proposed by Pring and Stjernström.⁷¹ On prolonged treatment with boiling hydrobromic acid, however, the biphenyldiol **58** yielded the dibenzofuran **59**, isolated as its tetra-*O*-methyl ether, as the major product and none of the alternative symmetrical isomer **60**. This was rationalized by arguing that compound **59** was the thermodynamically most stable product because of the smaller steric effect at the 1- and 9-positions compared with compound **60**.¹²

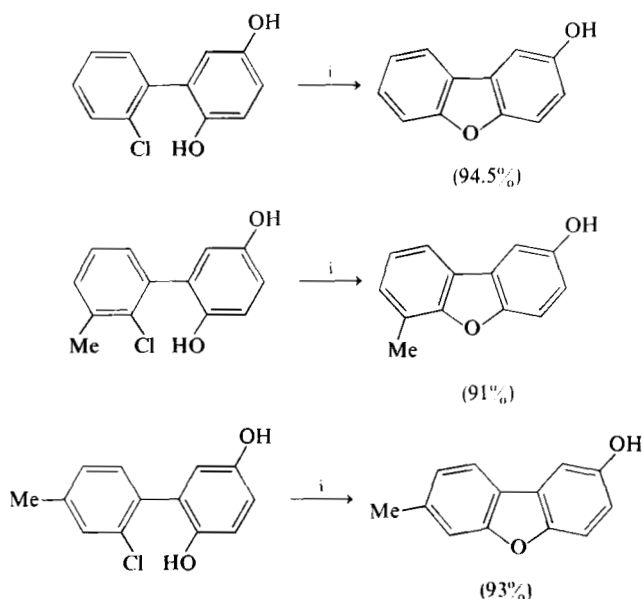
2. By Intramolecular Nucleophilic Substitution

There are a number of syntheses of dibenzofurans of the type shown in Scheme 11 that are usually carried out under basic conditions where X is a variety of leaving groups. A convenient synthesis of 2-dibenzofuranols

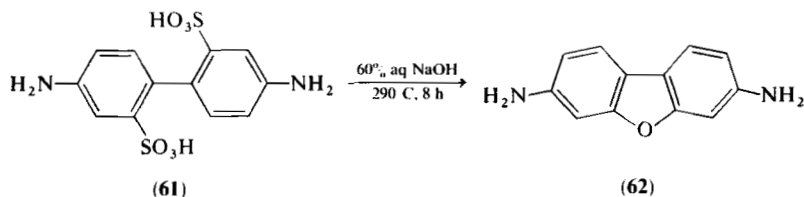


SCHEME 11

has been described by Schimmelschmidt.⁹¹ It involves arylation of 1,4-benzoquinone with the diazonium salts of 2-chloroanilines in buffered solution and reduction of the products to 2'-chloro-2,5-biphenyldiols. These on treatment with hydroxide in the presence of bisulfite at elevated temperatures and pressures afford good yields of 2-dibenzofuranols. It has been applied to the synthesis of a wide range of 2-dibenzofuranols,^{91,92} and some examples are shown in Scheme 12.⁹¹



SCHEME 12. Reagents: i, aq KOH, NaHSO₃, 190–230 C, 12–23 atm, 7 h.



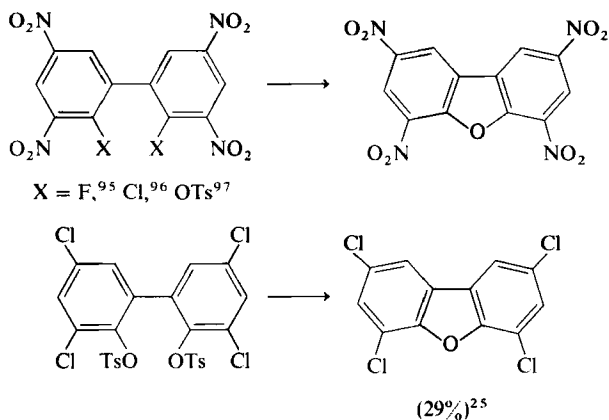
SCHEME 13

Benzidine-2,2'-disulfonic acid (**61**) affords the diamine **62** (Scheme 13) on treatment with aqueous sodium hydroxide.^{25,91}

⁹¹ K. Schimmelschmidt, *Justus Liebigs Ann. Chem.* **566**, 184 (1950).

⁹² H. O. Wirth, G. Waese, and W. Kern, *Makromol. Chem.* **86**, 139 (1965).

In the case of better leaving groups than chloride, or when the leaving group is activated by electron-withdrawing groups, ring closure occurs under milder conditions. Thus 2-acetoxy-2'-iodobiphenyl undergoes quantitative cyclization to dibenzofuran on boiling with aqueous molar sodium hydroxide,⁹³ and 2',3',4',5',6'-pentafluoro-2-biphenylol is cyclized to 1,2,3,4-tetrafluorodibenzofuran (85%) on treatment with potassium carbonate in boiling DMF.⁹⁴ 2,2'-Dihalobiphenyls or the analogous tosylates (Scheme 14) may also be cyclized under mild conditions in the presence of activating groups.^{25,95-97} 2,2'-Diacetoxybiphenyls activated by nitro and halo substituents are reported to undergo ring closure on heating with a dry mixture of barium and sodium carbonates.⁹⁸



SCHEME 14

Surprisingly, the 2,2'-biphenyldiol **63** (Scheme 15) is reported to produce some of the dibenzofuran **64** on methylation with methyl sulfate or iodo-methane in acetone in the presence of potassium carbonate.⁹⁹

Chlorination of 2-biphenylol under certain conditions can result in the formation of octachlorodibenzofuran.¹⁰⁰ The 2-biphenylol **65** (Scheme 16) on heating to 230–260°C produces the dibenzofurans **66** and **67**.¹⁰¹

⁹³ R. C. Fuson and R. L. Albright, *J. Am. Chem. Soc.* **81**, 487 (1959).

⁹⁴ P. J. N. Brown, R. Stephens, and J. C. Tatlow, *Tetrahedron* **23**, 4041 (1967).

⁹⁵ H. Zahn and H. Zuber, *Chem. Ber.* **86**, 172 (1953).

⁹⁶ F. H. Case and R. H. Schock, *J. Am. Chem. Soc.* **65**, 2086 (1943).

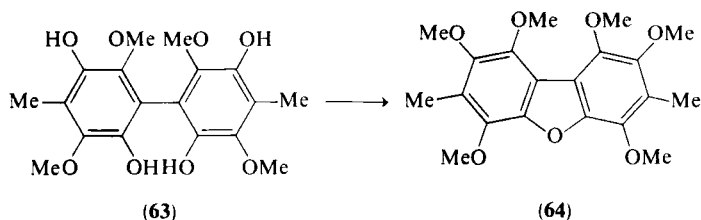
⁹⁷ W. Borsche and B. G. B. Scholten, *Ber. Dtsch. Chem. Ges.* **50**, 596 (1917).

⁹⁸ S. Yamashiro, *Bull. Chem. Soc. Jpn.* **17**, 10 (1942) [*CA* **41**, 4487 (1947)].

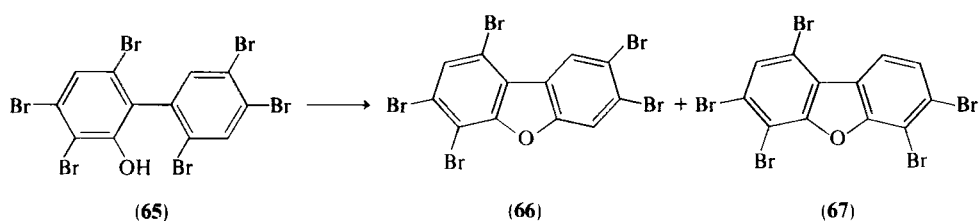
⁹⁹ G. Lloyd, A. Robertson, G. B. Sankey, and W. B. Whalley, *J. Chem. Soc.*, 2163 (1955).

¹⁰⁰ A. Gara, C.-A. Nilsson, and K. Andersson, *Chemosphere* **9**, 175 (1980).

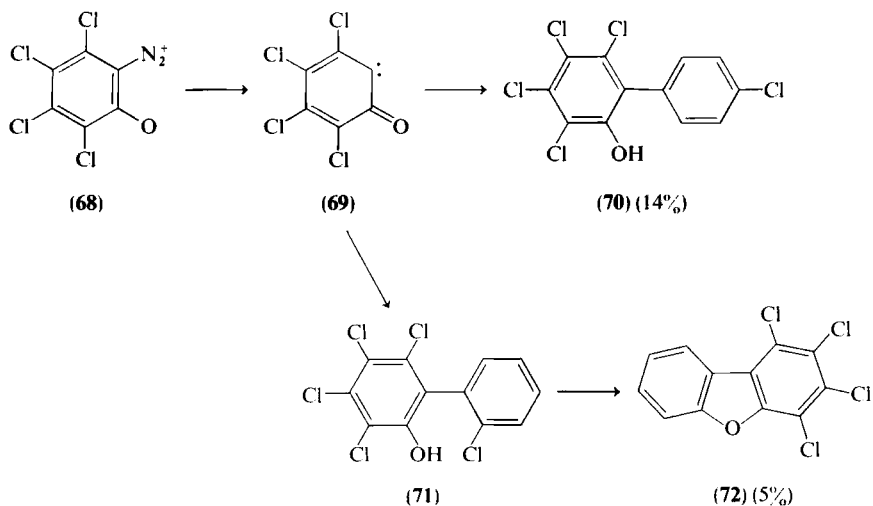
¹⁰¹ A. M. Gardner, V. L. Warren, J.-Y. T. Chen, and E. P. Mazzola, *J. Agric. Food Chem.* **27**, 116 (1979).



SCHEME 15



SCHEME 16



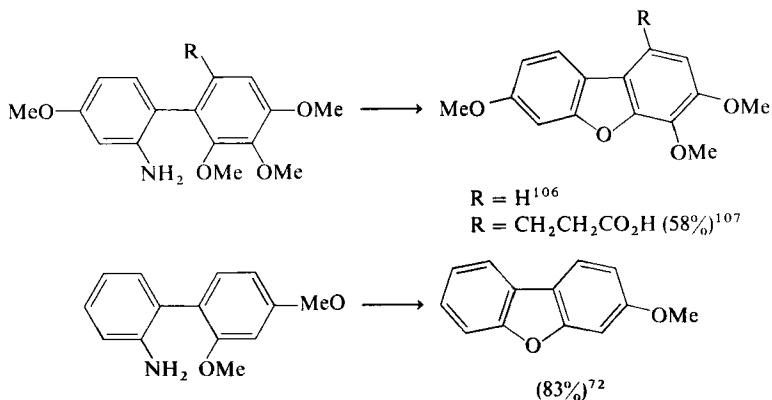
SCHEME 17

Decomposition of 3,4,5,6-tetrachlorobenzene-2-diazo 1-oxide (**68**, Scheme 17) in chlorobenzene at 130°C presumably involves the ketocarbene **69** and yields some of the dibenzofuran **72** via the 2'-chloro-2-biphenylol **71** because its isomer (**70**) is also a product.¹⁰²

¹⁰² R. Huisgen, G. Binsch, and H. König, *Chem. Ber.* **97**, 2884 (1964).

3. From 2'-Methoxy-2-biphenylamines

When 2'-methoxy-2-biphenylamine is diazotized in fluoroboric acid, an 85% yield of solid 2'-methoxy-2-biphenyldiazonium tetrafluoroborate is produced. On heating in dry benzene, this salt loses nitrogen and provides *O*-methyl dibenzofuranium tetrafluoroborate as an unstable solid. The latter salt, on account of the low basicity of dibenzofuran, reacts with a range of nucleophiles that undergo methylation with the release of dibenzofuran. Pyridine and pentachloropyridine are N-methylated, benzo[*b*]thiophene is S-methylated, and tetrahydrofuran and phenetole are O-methylated.¹⁰³ Thus it is no surprise that diazotization of 2'-methoxy-2-biphenylamine, followed by boiling of the diazonium salt in acidic solution, provides dibenzofuran in 90% yield.¹⁰⁴ The scope of this method of dibenzofuran synthesis (Scheme 18) has been little explored probably because of the difficulty of preparing the requisite biphenyls, which is usually accomplished by a crossed Ullmann reaction. A similar synthesis of xanthenes from 2-amino-2'-methoxybenzophenones is known.¹⁰⁵



SCHEME 18

2'-Phenoxy-2-biphenylamine, on diazotization and treatment with sulfuric acid, is reported to yield the *O*-phenyldibenzofuranium salt.¹⁰⁸

¹⁰³ A. J. Copson, H. Heaney, A. A. Logun, and R. P. Sharma, *JCS Chem. Commun.*, 315 (1972).

¹⁰⁴ L. Mascarelli and M. Pirona, *Gazz. Chim. Ital.* **68**, 117 (1938).

¹⁰⁵ F. Ullmann and W. Denzler, *Ber. Dtsch. Chem. Ges.* **39**, 4332 (1906).

¹⁰⁶ D. S. Tarbell, H. R. Frank, and P. E. Fanta, *J. Am. Chem. Soc.* **68**, 502 (1946).

¹⁰⁷ P. E. Fanta, *J. Am. Chem. Soc.* **70**, 4602 (1948).

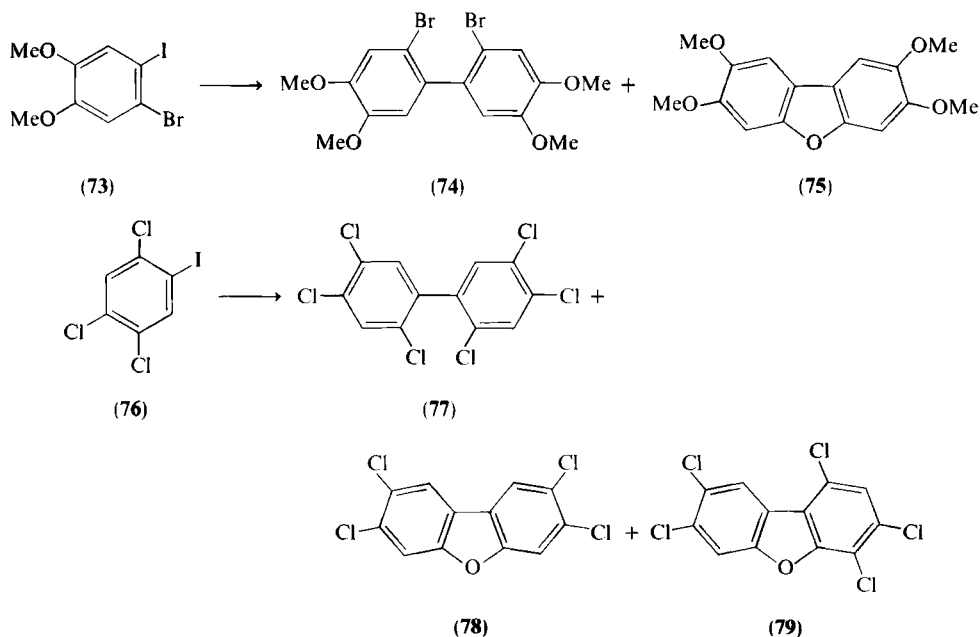
¹⁰⁸ A. N. Nesmeyanov and T. P. Tolstaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 647 (1959) [*CA* **53**, 21796 (1959)]

4. From 2,2'-Biphenyldiamines

When 2,2'-biphenyldiamines are tetrazotized and the resulting salts are heated, benzofurans are obtained, but benzo[*c*]cinnolines may be by-products.¹ This method has been little used.¹⁰⁹ 2,3,7,8-Tetramethyldibenzofuran (**47**) has been obtained in 40% yield from 4,4',5,5'-tetramethyl-2,2'-biphenyldiamine by this method.^{64,110}

5. By Ullmann-Type Synthesis

Baker and co-workers¹¹¹ observed during the synthesis of the biphenyl **74** (Scheme 19) from the iodo compound **73** by the Ullmann reaction at 230°C with copper bronze in nitrobenzene that the dibenzofuran **75** (1%)



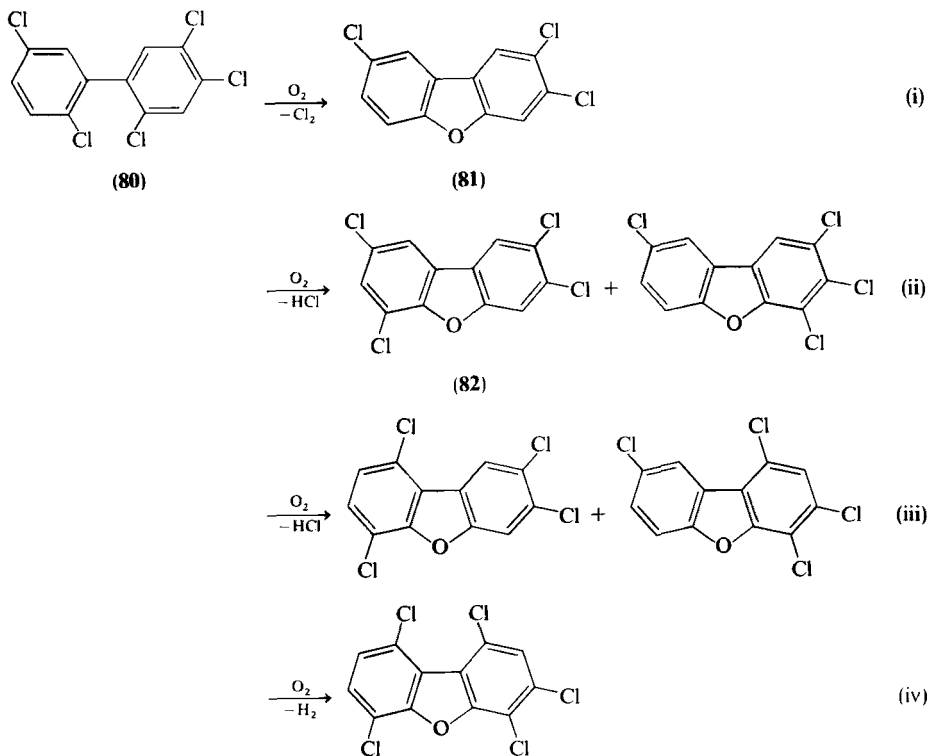
SCHEME 19

¹⁰⁹ I. Puskas, E. K. Fields, and E. M. Banas, *Prepr. Div. Petrol. Chem., Am. Chem. Soc.* **17**, B56 (1972) [*CA* **79**, 137068 (1973)].

¹¹⁰ I. Puskas and E. K. Fields, U.S. Patent 4,046,779 [*CA* **88**, 106183 (1978)].

¹¹¹ W. Baker, J. W. Barton, J. F. W. McOmie, R. J. Penneck, and M. L. Watts, *J. Chem. Soc.*, 3986 (1961).

was also obtained. When the reaction time was lengthened from 0.5 to 4 h, the yield of dibenzofuran increased to 8%. These authors suggested that the ring oxygen came from the solvent. However, 2-chloro-1-iodobenzene produced 3% dibenzofuran as well as the expected biphenyl,¹¹² and the iodo compound **76** (Scheme 19) gave the dibenzofuran **78** (3%) as well as the biphenyl **77**¹¹³ under the conditions of the Ullmann reaction in the absence of a solvent. In the absence of air, no dibenzofuran was obtained from 2-chloro-1-iodobenzene.¹¹²



SCHEME 20

The pyrolysis of 18 polychlorobiphenyls has been studied at 600°C in presence of air, and the polychlorodibenzofurans produced (0.1 to several percent) have been analyzed by GC-MS techniques,⁶ although many of the structural assignments are only tentative. Four types of reaction have been uncovered in this process, and they are shown in Scheme 20 for the pyrolysis

¹¹² M. Nilsson, *Acta Chem. Scand.* **12**, 537 (1958).

¹¹³ M. Moron, G. Sundström, and C. A. Wachtmeister, *Acta Chem. Scand.* **27**, 3121 (1973).

of 2,2',4,5,5'-pentachlorobiphenyl (**80**): (i) the formal loss of chlorine from the ortho positions of a 2,2'-dichlorobiphenyl, (ii) the formal loss of hydrogen chloride from a 2,2'-dichlorobiphenyl with a 2,3-chlorine shift, (iii) the formal loss of hydrogen chloride from a 2-chloro-2'-unsubstituted biphenyl, and (iv) the formal loss of hydrogen from the ortho positions of a 2,2'-unsubstituted biphenyl. In the above case only the structures of the major products **81** and **82** have been assigned with any degree of certainty. The source of the ring oxygen is presumably atmospheric oxygen, but its mode of incorporation is unknown.

Results analogous to the above have been obtained in the Ullmann synthesis of polychlorobiphenyls from polychloriodobenzenes at 220°C when by-product polychlorodibenzofurans (~0.1%) are produced.¹¹⁴ Routes (i) and (iii) appear to operate under these conditions. Thus the dichloriodobenzene **76** gave the tetrachlorodibenzofuran **78** by route (i), and in addition and in contrast to the results of Moron *et al.*,¹¹³ a pentachlorodibenzofuran, tentatively assigned structure **79** (Scheme 19), was detected.¹¹⁴

Polychlorodibenzofurans are also formed in trace amounts on pyrolysis of polychlorobenzenes at 620°C in sealed ampoules in the presence of air.¹¹⁵

C. BY ANNEALATION OF BENZOFURANS

1. Methods Involving Ketenes

2-Methylbenzofuran-3-carbaldehydes undergo ready condensation with Meldrum's acid (isopropylidene malonate) to afford arylmethylene derivatives **83**.¹¹⁶⁻¹¹⁸ These on flash vacuum pyrolysis at 500-600°C give 3-dibenzofuranols **84** (Scheme 21). The arylmethylene derivative, e.g., **85**, presumably undergoes conversion to a methylene ketene (**86**, Scheme 22) on pyrolysis, which undergoes a [1,5-*H*] shift and subsequent cyclization and tautomerization, yielding the dibenzofuranol **87**. The derived methyl ether **88**¹¹⁸ has been converted by mild acetylation with acetyl chloride and aluminum chloride and subsequent boron trichloride-induced demethylation to the natural product ruscodibenzofuran (**8**).¹³ A limitation is imposed on this method because 3-acetyl-2-methyldibenzofurans fail to condense with Meldrum's acid so that 1-methyl-3-dibenzofuranols are not available by this method.¹¹⁷

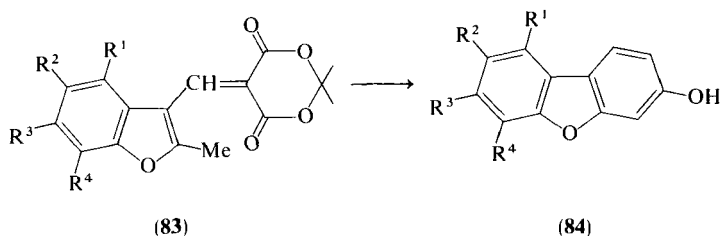
¹¹⁴ M. Morita, J. Nakagawa, and K. Akiyama, *Bull. Environ. Contam. Toxicol.* **18**, 200 (1977).

¹¹⁵ H. R. Buser, *Chemosphere* **8**, 415 (1979).

¹¹⁶ G. J. Baxter, R. F. C. Brown, and G. L. McMullen, *Aust. J. Chem.* **27**, 2605 (1974).

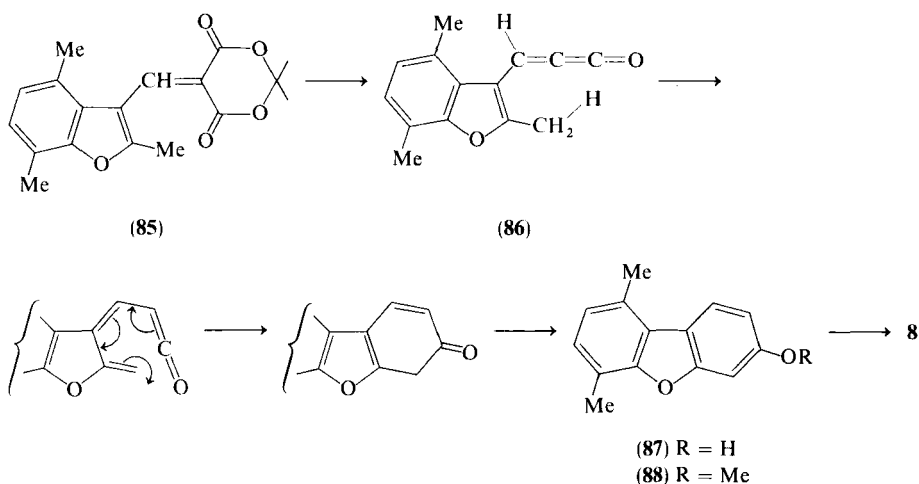
¹¹⁷ G. J. Baxter and R. F. C. Brown, *Aust. J. Chem.* **28**, 1551 (1975).

¹¹⁸ R. F. C. Brown and C. M. Jones, *Aust. J. Chem.* **33**, 1817 (1980).



R ¹	R ²	R ³	R ⁴	Yield (%)
H	OMe	H	H	83
Me	H	OMe	H	28
Me	H	H	Me	82

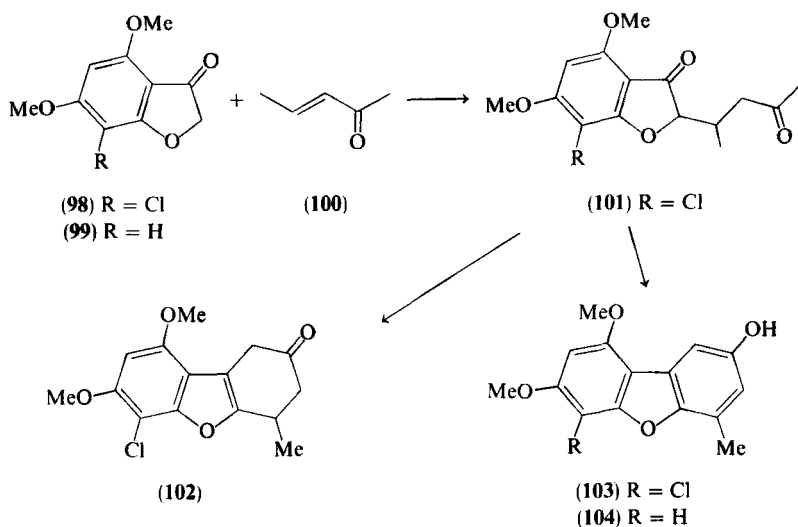
SCHEME 21



SCHEME 22

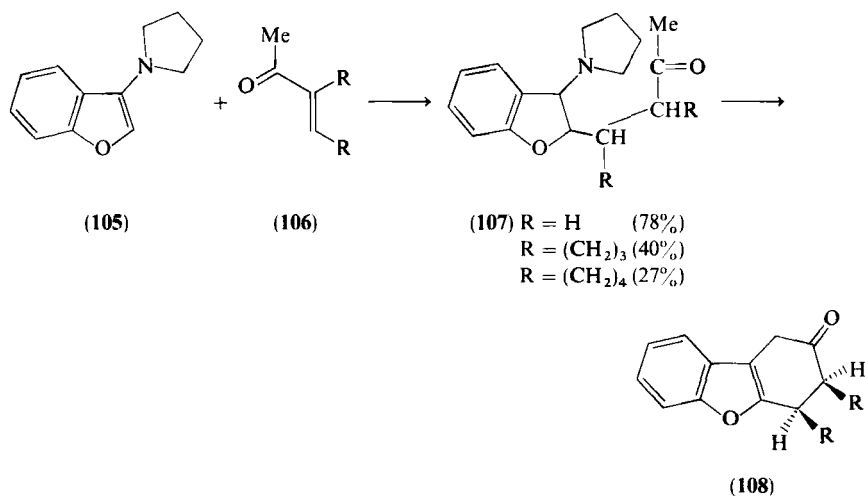
A similar synthesis of mechanistic interest rather than preparative value involves the thermal reaction of dimethyl 2,5-bisdiazo-3,4-diketoadipate (**89**, Scheme 23) with benzofuran (**91**).¹¹⁹ The presumed intermediate is the pyrone cation **90** produced from the adipate **89** by the Wolff rearrangement, cyclization, and loss of nitrogen. Electrophilic substitution then affords the benzofuran **92**, which can be isolated. Ring opening and cyclization of the resultant ketene **93** then affords the dibenzofuran **94** in poor (0.4%) yield.

¹¹⁹ C. W. Bird, C. K. Wong, D. Y. Wong, and F. L. K. Koh, *Tetrahedron* **32**, 269 (1976).



SCHEME 25

similar method.¹²² 7-Methoxy-4,9-dimethyl-2-dibenzofuranol has also been synthesized by this method,²⁰ except that palladized charcoal was used to dehydrogenate the intermediate tetrahydro-2-dibenzofuranone.



SCHEME 26

¹²² J. MacMillan, T. P. C. Mulholland, A. W. Dawkins, and J. Ward, *J. Chem. Soc.*, 429 (1954).

The enamine 3-(1-pyrrolidinyl)benzofuran (**105**, Scheme 26), reacts with α,β -unsaturated ketones (**106**) in boiling benzene to produce the adducts **107**, which on exposure to an ethanolic acetate buffer at room temperature provide the tetrahydro-2-dibenzofuranones **108**.¹²³

3. By Intramolecular Friedel–Crafts Reaction

4-(2'-Benzofuranyl)butanoic acid readily forms the acid chloride, and this undergoes intramolecular Friedel–Crafts acylation on treatment with tin(IV) chloride in carbon disulfide at room temperature, providing 1,2,3,4-tetrahydro-1-dibenzofuranone (54%).¹²⁴ This intermediate has been converted to dibenzofuran by lithium aluminum hydride reduction and subsequent dehydrogenation, to 1-methyldibenzofuran by Grignard reaction and dehydrogenation, and to 1-dibenzofuranol by reaction with *N*-bromosuccinimide and subsequent dehydrobromination with pyridine.

Benzofuran-2-carbaldehydes readily undergo Wittig reactions in tetrahydrofuran at room temperature with the resonance-stabilized ylide 2-carboxy-1-methoxycarbonyl ethyltriphenylphosphorane, affording high yields of (*E*)-4-(2-benzofuranyl)-3-methoxycarbonylbut-3-enoic acids. This method is preferable to the Stobbe condensation. The Stobbe-type intermediates undergo quantitative cyclization to methyl 1-acetoxydibenzofuran-3-carboxylates on exposure to acetic anhydride at 100°C. Examples are shown in Scheme 27. The intermediate **109** has been used in a synthesis of cannabifuran (**110**),²⁴ and the intermediate **111** has been used in a synthesis of the lichen metabolite schizopeltic acid (**112**).²³

Intramolecular Friedel–Crafts reactions have also been used to synthesize benzannelated dibenzofurans.^{125,126}

4. By Intramolecular Claisen Condensation

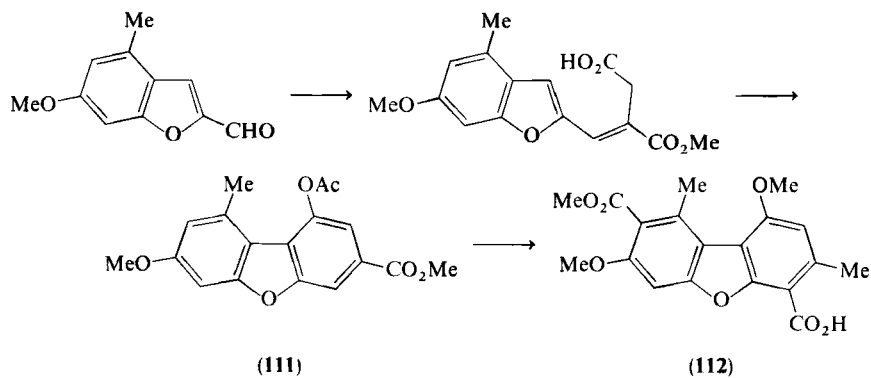
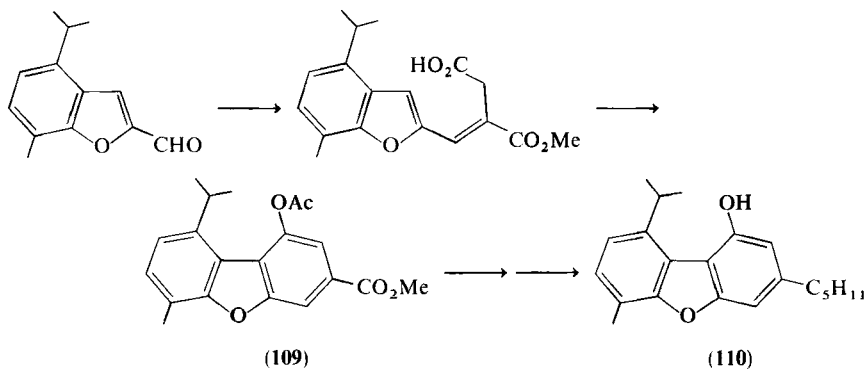
Methyl 2-(2'-benzofuranyl)acetate (**113**, Scheme 28) readily undergoes Friedel–Crafts acylation with acid chlorides and tin(IV) chloride, affording high yields of the 3-acyl derivatives **114**. On treatment with boiling methanolic sodium methoxide under nitrogen, these intermediates undergo intramolecular cyclization, with loss of methanol, affording 1,3-dibenzofurandiols **115**. The 2-(3'-acyl-2'-benzofuranyl)acetic esters (**114**) behave as vinylogous β -ketoesters and may be methylated on C-2 of the acetic ester side chain by treatment with iodomethane and potassium carbonate in DMF

¹²³ M. Schaeffer, J. Weber, and P. Faller, *Synthesis*, 122 (1979).

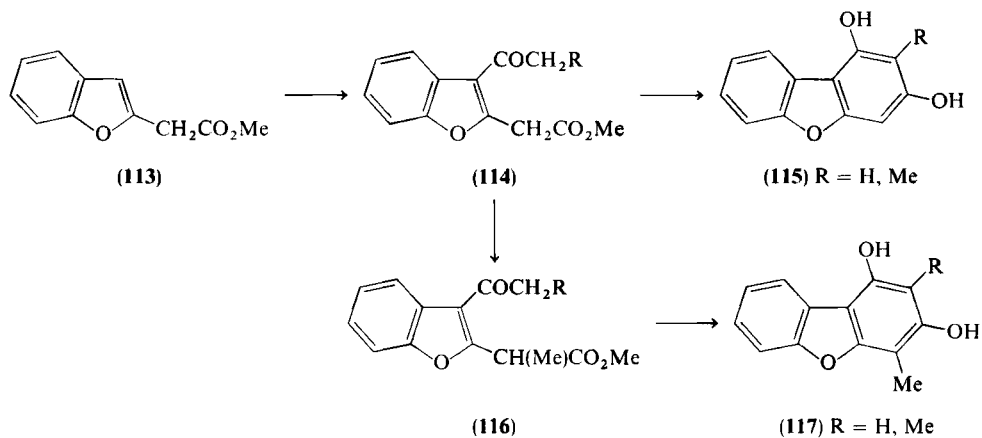
¹²⁴ J. N. Chatterjea, *J. Indian Chem. Soc.* **34**, 306 (1957).

¹²⁵ J. N. Chatterjea, *J. Indian Chem. Soc.* **32**, 263 (1955).

¹²⁶ P. M. Chakrabarti, *Tetrahedron Lett.*, 1771 (1963).

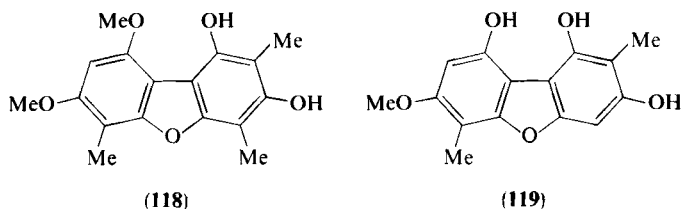


SCHEME 27

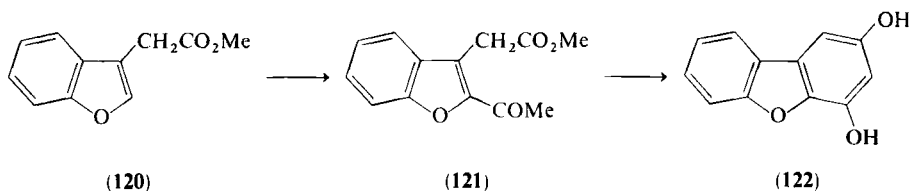


SCHEME 28

at room temperature, thus affording the products **116**. This behavior is no doubt due to the inductive effect of the ring oxygen because the isomeric 2-(2'-acyl-3-benzofuranyl)acetic esters cannot be similarly alkylated. The intermediates **116** also readily undergo cyclization to 4-methyl-1,3-dibenzofurandiols (**117**). This method has been used for the synthesis of the heavily substituted dibenzofurans **118** and **119**.



Methyl 2-(2'-acetyl-3'-benzofuranyl)acetate (**121**), available by Friedel-Crafts acetylation of methyl 2-(3'-benzofuranyl)acetate (**120**, Scheme 29), on treatment with boiling methanolic sodium methoxide affords 2,4-dibenzofurandiol (**122**).²²



SCHEME 29

5. From 2-Vinylbenzofurans by Diels-Alder Reaction

Elix and co-workers in a series of papers^{34,127-131} have examined the Diels-Alder reactions between 2-vinylbenzofurans and both ethylenic and acetylenic dienophiles. The former type of reaction, first observed by Kamthong and Robertson,¹³² generally results in good yields of tetrahydrodibenzofurans, and the autoxidation¹³⁰ and stereochemistry¹³¹ of the products have been studied. Acetylenic dienophiles often give dibenzofurans directly.^{34,127,128}

¹²⁷ J. D. Brewer, W. J. Davidson, J. A. Elix, and R. A. Leppik, *Aust. J. Chem.* **24**, 1883 (1971).

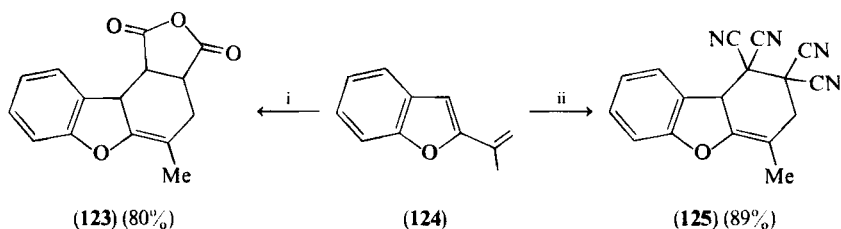
¹²⁸ J. D. Brewer and J. A. Elix, *Aust. J. Chem.* **25**, 545 (1972).

¹²⁹ J. A. Elix and D. Tronson, *Aust. J. Chem.* **26**, 1093 (1973).

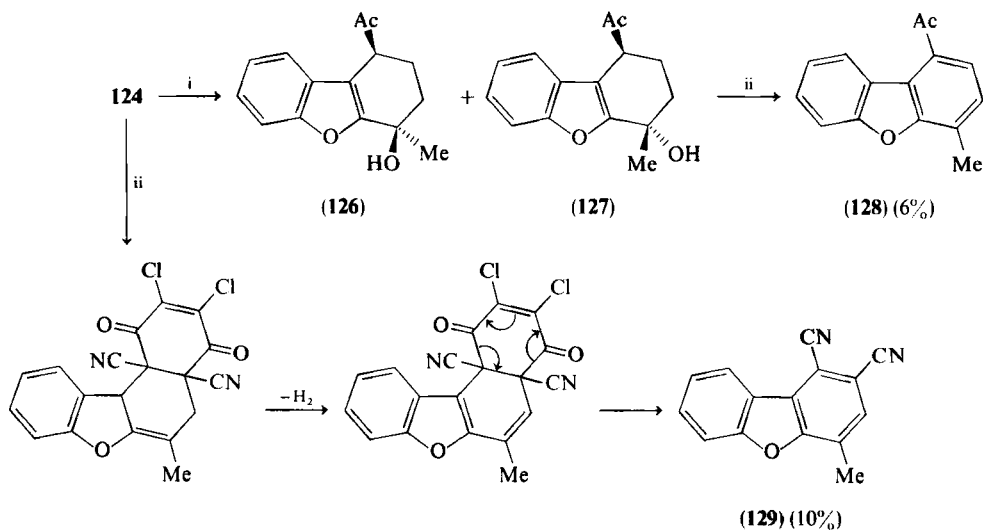
¹³⁰ J. D. Brewer and J. A. Elix, *Aust. J. Chem.* **28**, 1059 (1975).

¹³¹ J. D. Brewer and J. A. Elix, *Aust. J. Chem.* **28**, 1083 (1975).

¹³² B. Kamthong and A. Robertson, *J. Chem. Soc.*, 925, 933 (1939).



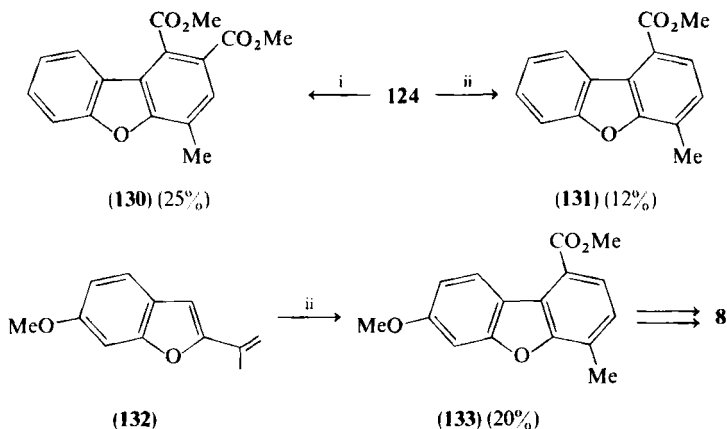
SCHEME 30. Reagents: i, maleic anhydride, benzene, Jf , 2.5 d; ii, TCNE, CHCl_3 , 25°C, 12 h.



SCHEME 31. Reagents: i, $\text{CH}_2=\text{CHCOMe}$, benzene, Jf , 4 d; ii, DDQ, benzene, Jf , 4 d.

2-Isopropenylbenzofuran (**124**, Scheme 30) affords good yields of the adducts **123** and **125** on separate reaction with maleic anhydride and tetracyanoethylene.³⁴ With but-3-en-2-one, 2-isopropenylbenzofuran (**124**, Scheme 31) affords the adducts **126** and **127** in a combined yield of 29%. When the crude product was dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in boiling benzene, the aromatized product **128** (6%) was obtained. It was accompanied by the dicyanodibenzofuran **129**, which was found to arise from the excess diene present in the reaction mixture. A speculative mechanism is shown.¹³⁰

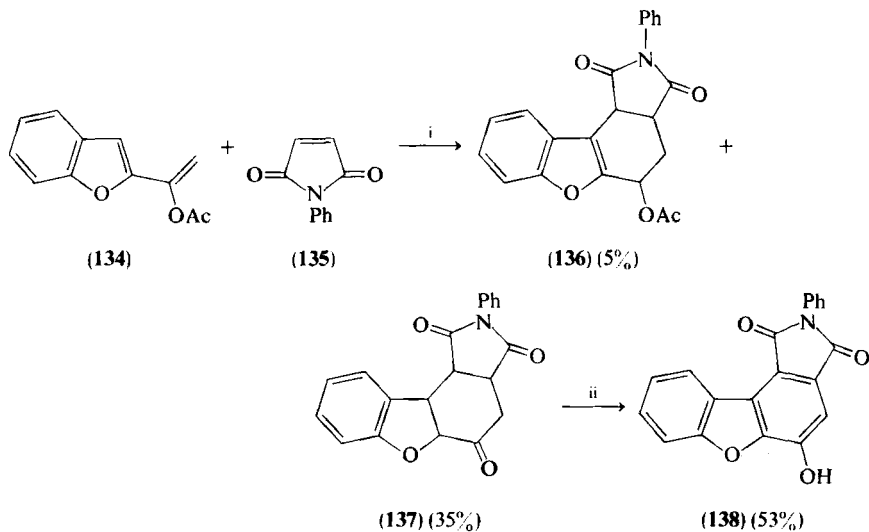
2-Isopropenylbenzofuran (**124**), on reaction with dimethyl acetylenedicarboxylate, affords the dibenzofuran **130** (Scheme 32), the intermediate dihydrodibenzofuran undergoing dehydrogenation at the expense of the diene in as much as some 2-isopropylbenzofuran was isolated. Methyl propiolate similarly afforded the dehydrogenated adduct **131**.³⁴ Advantage has been



SCHEME 32. Reagents: i, DMAD, benzene, Jf , ii, $\text{HC}\equiv\text{CCO}_2\text{Me}$, PhMe, Jf .

taken of the regiospecificity of the latter type of reaction in a synthesis of ruscodibenzofuran (**8**).¹³³ The isopropenylbenzofuran **132** afforded the aromatized adduct **133**, which on simple functional group transformation, acylation, and demethylation gave ruscodibenzofuran (**8**) in 14% overall yield.

The enol acetate **134** (Scheme 33), on reaction with *N*-phenylmaleimide (**135**) and isolation by chromatography from the crude product, gave the

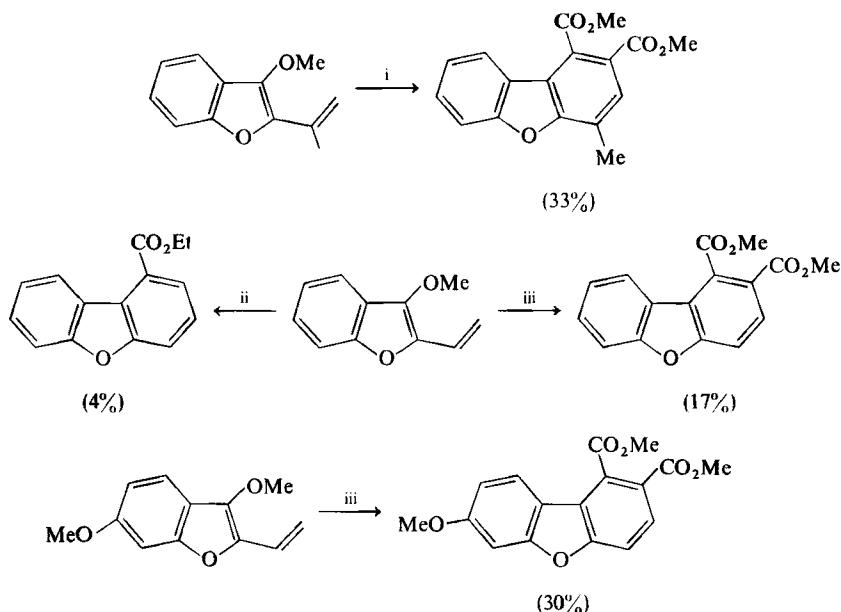


SCHEME 33. Reagents: i, PhMe, Jf , N_2 , 3 d; ii, Pd/C, C_{10}H_8 , Jf .

¹³³ R. T. Scannell and R. Stevenson, *JCS Chem. Commun.*, 1103 (1980).

adduct **136**, in which the double bond has moved into conjugation, and the adduct **137**, in which the enol acetate has undergone hydrolysis. This last compound was dehydrogenated to the dibenzofuran **138** with palladized charcoal.¹³⁰

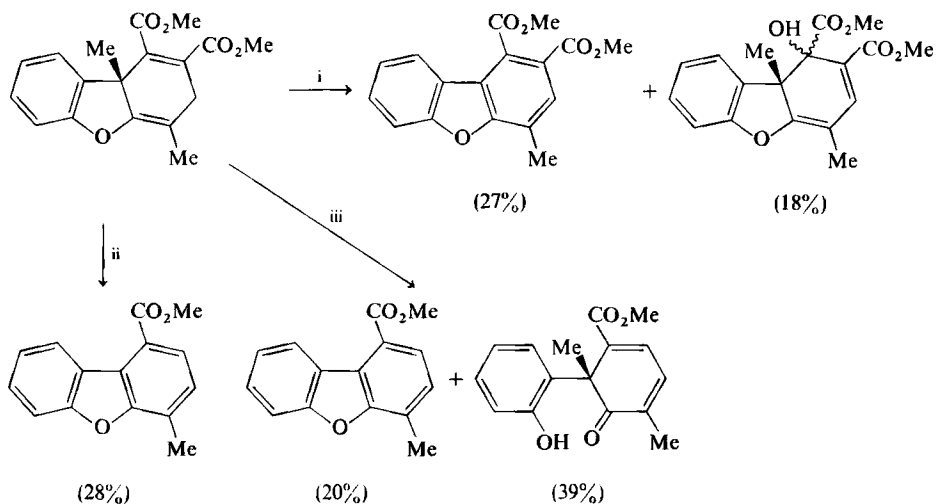
3-Methoxy-2-vinylbenzofurans (Scheme 34) afford dibenzofurans on reaction with acetylenic dienophiles; the intermediate adducts undergo elimination of methanol *in situ*, but the yields are poor.¹²⁷



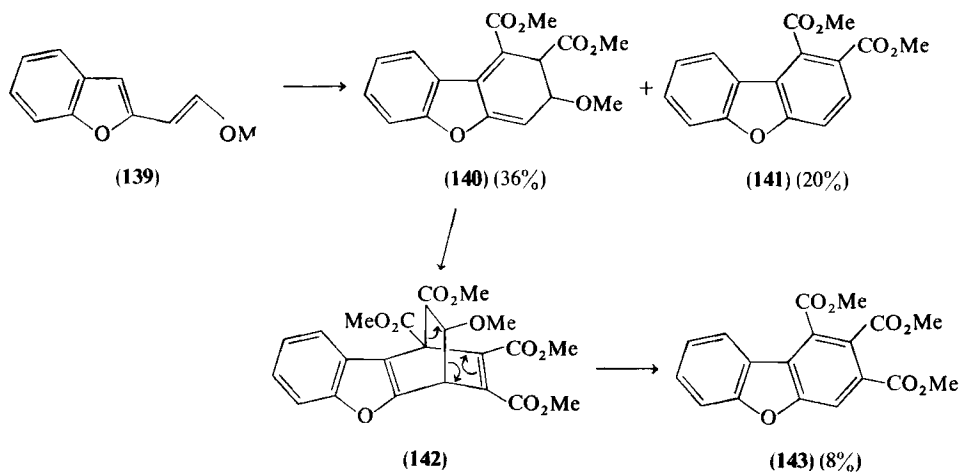
SCHEME 34. Reagents: i, DMAD, xylene, $\uparrow\uparrow$, 1.5 h; ii, $\text{HC}\equiv\text{CCO}_2\text{Et}$, $\text{Cl}_2\text{CHCHCl}_2$, $\uparrow\uparrow$, 1 d; iii, DMAD, PhMe, $\uparrow\uparrow$, 1–3 d.

3-Methyl-2-vinylbenzofurans also undergo cycloaddition with acetylenic dienophiles, but ready aromatization of the products is blocked by the angular methyl group. It can, however, be achieved by oxidizing agents, such as selenium dioxide or chromium trioxide, or even by exposure to air (Scheme 35).¹²⁹ Mechanisms for these reactions have been postulated.

In order to exploit the cycloaddition reactions of 2-vinylbenzofurans for natural product synthesis, the reactions of (*E*)-2-(β -methoxyvinyl)benzofurans have been examined. The simplest compound (**139**, Scheme 36) on reaction with dimethyl acetylenedicarboxylate in boiling toluene gave a mixture of products. The major adduct was not the one expected but was its conjugation product **140**. The diene system in **140** is able to react with

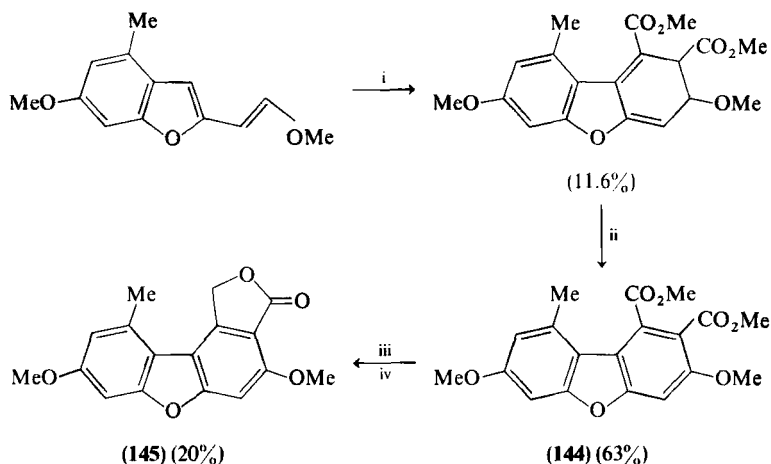


SCHEME 35. Reagents: i, SeO_2 , dioxane, \uparrow , 16 h; ii, CrO_3 , AcOH , 25°C , 3 h; iii, air, 16 h.



SCHEME 36

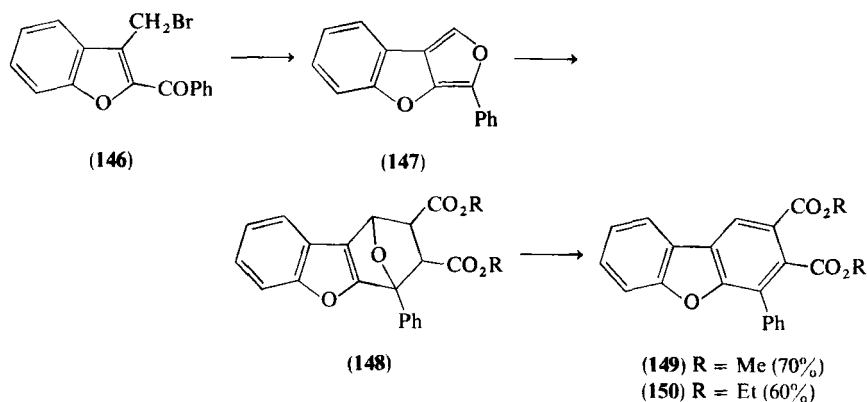
more of the acetylene, and the resultant adduct **142** undergoes retrodiene reaction, affording the triester **143**. The diester **141** presumably arises from the initial adduct or its conjugation product **140** by 1,4- or 1,2-elimination of methanol. The adduct **140** can be aromatized, with retention of the methoxy group, in 67% yield by dibenzoyl peroxide-initiated reaction with *N*-bromosuccinimide in boiling carbon tetrachloride. This method has been



SCHEME 37. Reagents: i, DMAD, PhMe, \uparrow , 14 h; ii, NBS, $(\text{PhCO})_2\text{O}_2$, CCl_4 , 5 min; iii, LAH, Et_2O ; iv, $\text{Na}_2\text{Cr}_2\text{O}_7$, aq dioxane, H^+ , 0–25°C, 3 h.

used in a synthesis of the di-*O*-methyl ether **145** (Scheme 37) of the lichen dibenzofuran strepsilin.¹²⁸ The steric effect of the 9-methyl group in the oxidation step is critical for its regiospecificity. When the oxidation of 1,2-bishydroxymethyl-4-methyldibenzofuran was carried out under similar conditions, the two possible lactones were obtained in equal yields. The intermediate **144** has also been prepared by reaction of (*E*)-3,6-dimethoxy-2-(β -methoxyvinyl)-4-methylbenzofuran with dimethyl acetylenedicarboxylate, but the yield was only 7.4%.

Heating the 3-bromomethyl-2-benzofuryl ketone **146** (Scheme 38) with dimethyl maleate or diethyl fumarate at 170°C produced the dibenzofurans

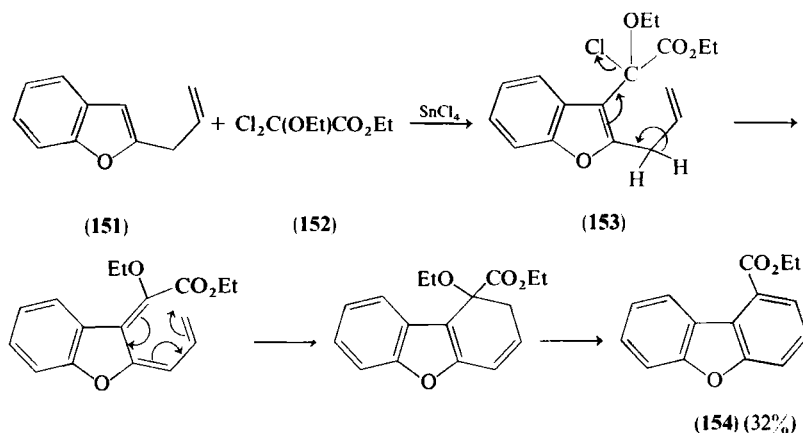


SCHEME 38

149 and **150**. The furo[3,4-*b*]benzofuran intermediate **147** may be trapped with dimethyl acetylenedicarboxylate as a dihydrodibenzofuran adduct, but the tetrahydrodibenzofuran **148** undergoes dehydration under the severe reaction conditions.¹³⁴ The sulfur and selenium analogs of compound **147** are isolable compounds and afford **149** on reaction with dimethyl acetylenedicarboxylate in boiling xylene.¹³⁵

6. Miscellaneous Methods

When 2-allylbenzofuran (**151**, Scheme 39) is allowed to react with ethyl (dichloro)ethoxyacetate (**152**) in the presence of tin(IV) chloride at -78°C , an electrophilic substitution occurs, and the intermediate **153**, after elimination of hydrogen chloride, undergoes an electrocyclic reaction, producing ethyl dibenzofuran-1-carboxylate (**154**).¹³⁶



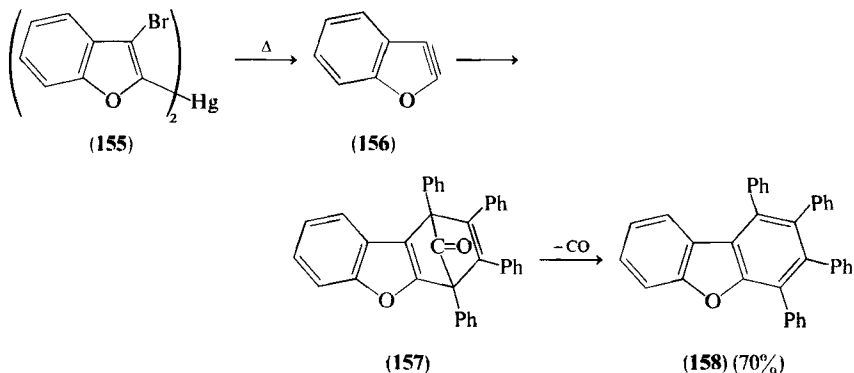
SCHEME 39

Benzofuran in boiling dioxane and acetic acid, in the presence of equimolar proportions of styrene and palladium(II) acetate, yields 2,3-diphenyl-dibenzofuran (26%) as well as 2-styryl- (16%) and 3-styrylbenzofuran (3%). The reaction presumably involves electrophilic substitution at the 2-position of benzofuran by palladium(II) acetate, followed by addition to the alkene and loss of palladium hydride. Further reaction at the 3-position of the resultant 2-styrylbenzofuran would yield an intermediate that could undergo

¹³⁴ A. Shafiee and E. Behmann, *J. Heterocycl. Chem.* **15**, 1459 (1978).

¹³⁵ A. Shafiee and E. Behmann, *J. Heterocycl. Chem.* **15**, 589 (1978).

¹³⁶ J. Ashby, M. Ayad, and O. Meth-Cohn, *JCS Perkin I*, 1744 (1974).



SCHEME 40

electrocyclization to the isolated dibenzofuran. Acrylonitrile reacted with benzofuran to produce only substitution products.¹³⁷

When the mercury derivative **155** (Scheme 40) is heated with tetraphenylcyclopentadienone, the dehydrobenzofuran **156** that is produced is trapped, and the initial adduct **157** is decarbonylated, thereby producing 1,2,3,4-tetraphenyldibenzofuran (**158**).¹³⁸

D. FROM QUINONES

1. By Diels–Alder Reaction

1,3-Cyclohexadienes are available by the methodology of Birch, and the reactions of 1-methoxy-,¹³⁹ 1,3-dimethoxy-,^{139,140} 1,3-bis(trimethylsilyloxy)-,¹⁴¹ and 1-methoxy-4-methyl-1,3-cyclohexadiene¹³⁹ with a number of 1,4-benzoquinones have been investigated. Acid treatment of the adducts and subsequent dehydrogenation provides a synthesis of 2-dibenzofuranols. Thus the adduct **159** (Scheme 41) from 1,4-benzoquinone and 1,3-dimethoxy-1,3-cyclohexadiene, on treatment with a trace of concentrated hydrochloric acid in ethanol at room temperature, affords the tetrahydrodibenzofuranone **161**. When the adduct **159** is heated under reflux in aqueous methanol, the reaction can be arrested at the dihydrodibenzofuran **160**. The tetrahydrodibenzofuranone **161** on dehydrogenation with palladized charcoal affords 2,7-dibenzofurandiol.¹³⁹

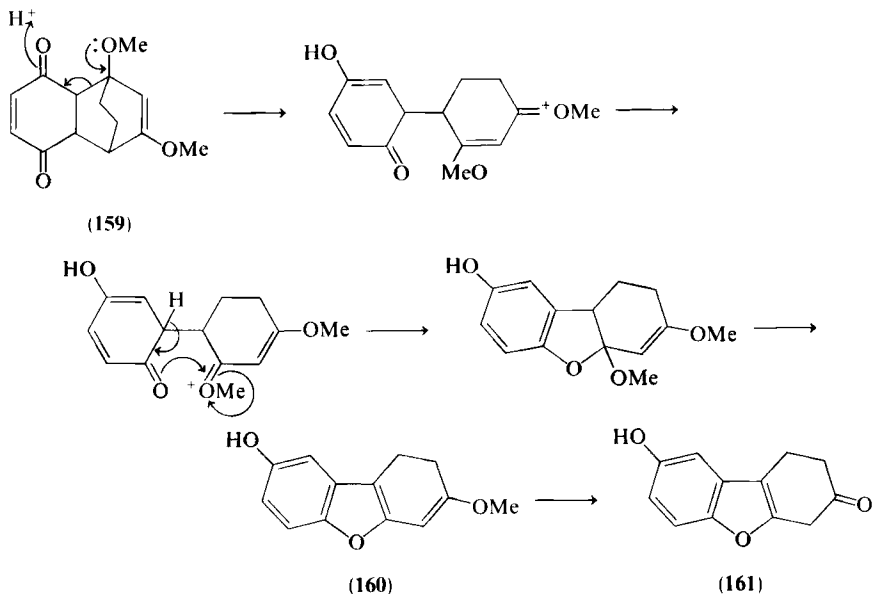
¹³⁷ Y. Fujiwara, O. Maruyama, M. Yoshidomi, and H. Taniguchi, *J. Org. Chem.* **46**, 851 (1981).

¹³⁸ G. Wittig, *Rev. Chim., Acad. Repub. Pop. Roum.* **7**, 1391 (1962) [*CA* **61**, 4297 (1964)].

¹³⁹ A. J. Birch, D. N. Butler, and J. B. Sidall, *J. Chem. Soc.*, 2932 (1964).

¹⁴⁰ R. G. F. Giles and G. H. P. Roos, *JCS Perkin I*, 2057 (1976).

¹⁴¹ K. Krohn, H.-H. Ostermeyer, and K. Tolkiehn, *Chem. Ber.* **112**, 2640 (1979).



SCHEME 41

2. By Acid Treatment

1,4-Benzoquinone undergoes oligomerization on treatment with mineral acids¹⁴²; the major crystalline product is a trimer, but tetramers and a dimer are also formed. Quinone-phenol coupling is thought to be involved in this reaction and the first step is accordingly the coupling of 1,4-benzoquinone with hydroquinone to produce the biphenyltetraol **162** (Scheme 42), which is oxidized by 1,4-benzoquinone to the internal quinhedrone **163**. Hemiketalization leads to **164**, which on protonation and loss of water gives the ion **165**, which is reduced by hydroquinone to the isolable dibenzofurandiol **166**. The ion **165**, by coupling with hydroquinone or reaction with benzoquinone, would lead to the other isolated products. The structures of the products have been verified by X-ray crystallography.¹⁴³

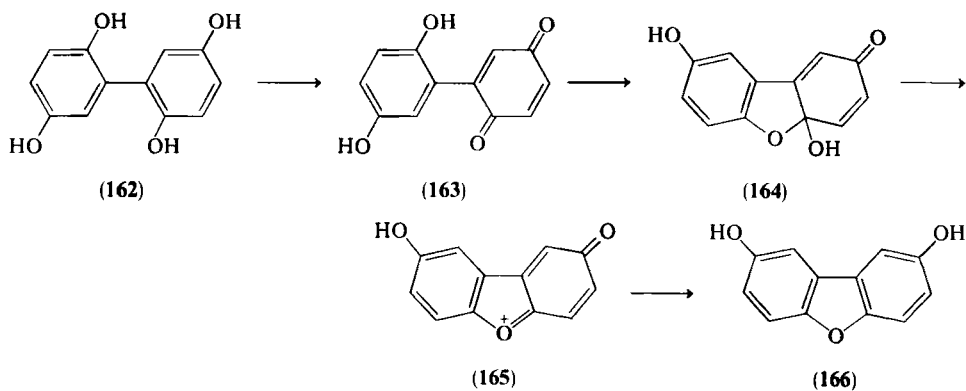
Treatment of 2-methoxy-1,4-benzoquinone with hydrogen chloride yields a highly colored compound formulated as the internal quinhedrone **167**,¹⁴⁴ which on further reaction with hydrogen chloride yields the dibenzofuran **168**.¹⁴⁵ 2-Methoxy-1,4-dihydroxybenzene is oxidized by 1,4-benzoquinone

¹⁴² H. Erdtman and H.-E. Högborg, *Tetrahedron* **35**, 535 (1979).

¹⁴³ J.-E. Berg, H. Erdtman, H.-E. Högborg, B. Karlsson, A.-M. Pilotti, and A.-C. Söderholm, *Tetrahedron Lett.*, 1831 (1977).

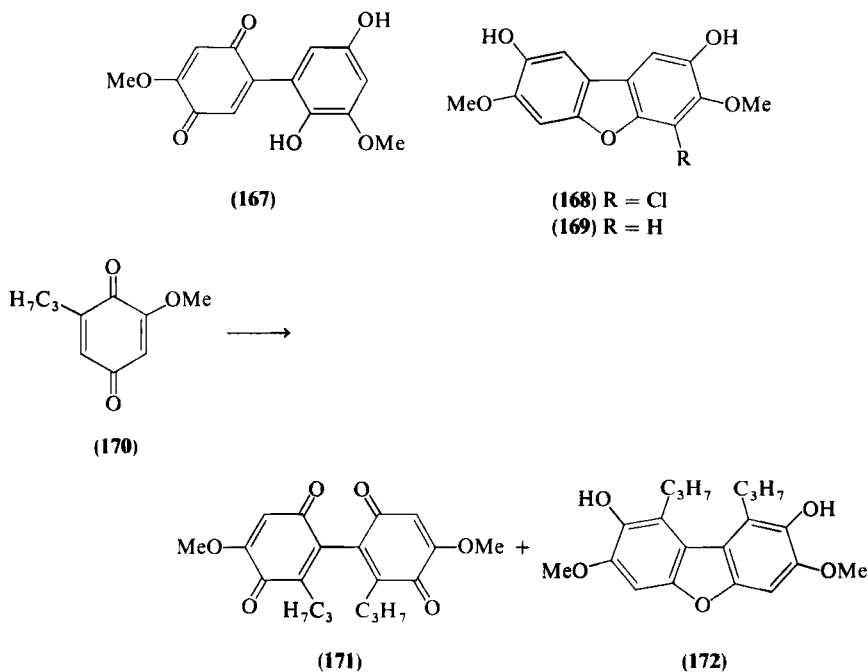
¹⁴⁴ H. G. H. Erdtman, *Proc. Soc. London, Ser. A* **143A**, 177 (1934) [*CA* **28**, 1337 (1934)].

¹⁴⁵ C. Brown, A. R. Forrester, and R. H. Thomson, *Tetrahedron* **29**, 3059 (1973).



SCHEME 42

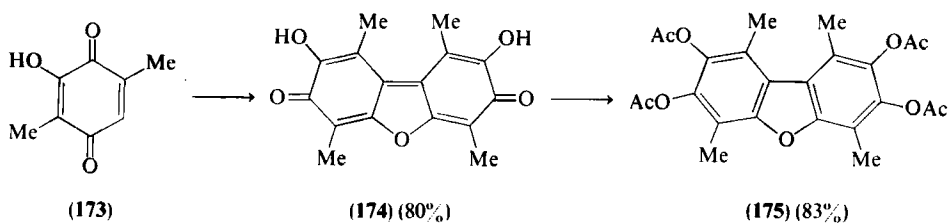
in aqueous acetic acid to the quinhydrone **167**, and the dibenzofuran **169** is also produced.¹⁴⁶ The dibenzofuran **169** presumably arises by a mechanism similar to that described above.



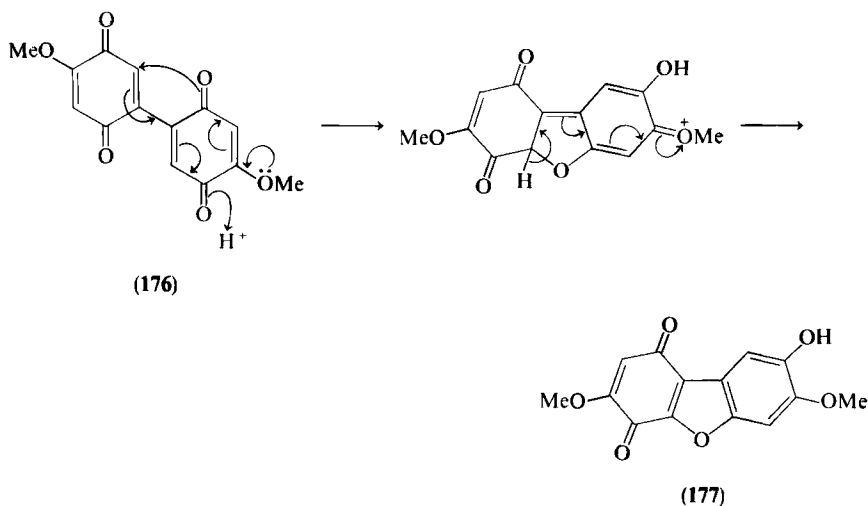
SCHEME 43

¹⁴⁶ L. Jurd, *Aust. J. Chem.* **33**, 1603 (1980).

2-Methoxy-6-propyl-1,4-benzoquinone (**170**, Scheme 43) with hydrogen chloride undergoes dimerization and yields the biquinone **171** and the dibenzofuran **172**.⁸⁴ 2-Hydroxy-3,6-dimethyl-1,4-benzoquinone (**173**, Scheme 44), however, on treatment with boron trifluoride etherate in ether, or with concentrated sulfuric acid in acetic acid at room temperature, yields the extended quinone **174**, which on reductive acetylation affords the dibenzofuran **175**.¹⁴⁷



SCHEME 44



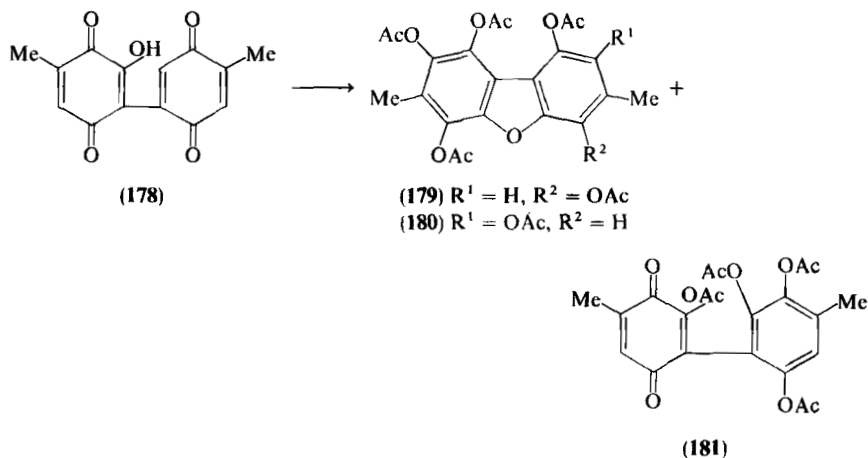
SCHEME 45

Biquinones may also be converted to dibenzofuran derivatives by a variety of methods. Thus the biquinone **176** (Scheme 45) is converted to the dibenzofuranquinone **177** on treatment with acid.¹⁴⁸ The same transformation of **176** and its analogs into dibenzofuranquinones may be effected thermally and

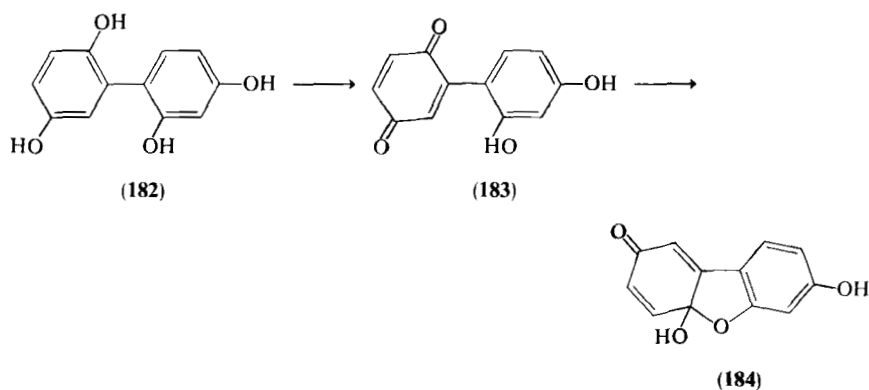
¹⁴⁷ H. Musso, U. v. Gizycki, U. I. Zahorsky, and D. Bormann, *Justus Liebigs Ann. Chem.* **676**, 10 (1964).

¹⁴⁸ H. G. H. Erdtman, *Proc. Soc. London, Ser. A* **143A**, 223 (1934) [*CA* **28**, 1338 (1934)].

photochemically.¹⁴⁹ The biquinone **176** can also be converted to bromo- and chlorodibenzofurans by action of the appropriate hydrogen halide.^{145,150} The biquinone **178** (Scheme 46) on Thiele acetylation affords **179** or **180** and **181**.¹⁵¹



SCHEME 46



SCHEME 47

¹⁴⁹ A. J. Shand and R. H. Thomson, *Tetrahedron* **19**, 1919 (1963).

¹⁵⁰ I. S. Joffe and A. F. Sukhina, *J. Gen. Chem. USSR (Engl. Transl.)* **23**, 1433 (1953).

¹⁵¹ T. Posternak, W. Alcalay, and R. Huguenin, *Helv. Chim. Acta* **39**, 1556 (1956).

1,4-Benzoquinone and its alkyl-substituted derivatives react with resorcinol under mild acidic conditions to afford dibenzofurans in variable yield. A mechanism similar to the one involved in the acid-catalyzed oligomerization of 1,4-benzoquinones has been proposed.^{152,153} Thus resorcinol reacts with 1,4-benzoquinone to produce the biphenyltetraol **182** (Scheme 47), which is oxidized by benzoquinone to the quinone **183**. Hemiketalization produces **184**, which undergoes the same fate as its analog **164**. Isolation of the dibenzofurans is usually achieved by methylation followed by chromatography. With 1,4-benzoquinone the yield of 2,7-dimethoxydibenzofuran is only 1%; 2-methyl-1,4-benzoquinone gave a mixture (9%) of 2,7-dimethoxy-3- and -4-methyldibenzofuran. With more highly substituted quinones the yields are better. Thus 2,6-dimethyl-1,4-benzoquinone supplies 2,7-dimethoxy-1,3-dimethyldibenzofuran (57%) and 2,3,5-trimethyl-1,4-benzoquinone affords 1,3,4-trimethyl-2,7-dibenzofurandiol (75%).¹⁵² This type of reaction has been used in a synthesis of ruscodibenzofuran (**8**).¹⁵⁴ Reaction of 2,5-dimethyl-1,4-benzoquinone (**185**) with 3-methoxyphenol (**186**), followed by acetylation, gave the dibenzofuran **187** (Scheme 48). The derived phenol **188** was converted to the tetrazole derivative **189**, which on hydrogenolysis gave the required intermediate **190** for the synthesis of ruscodibenzofuran (**8**).

Treatment of veratrole (**191**) with excess of 2,5-dichloro- (**192**) or 2,6-dichloro-1,4-benzoquinone in 70% sulfuric acid yields dibenzofurans and other products. Thus 2,5-dichloro-1,4-benzoquinone (**192**, Scheme 49) affords the dibenzofuran **193**, the diarylquinone **194** and the triphenylene **195**.¹⁵⁵ The quinol formed by acid-catalyzed addition of veratrole (**191**) to the quinone **192** is presumably oxidized to the arylquinone **196**, which can form the dibenzofuran **193** or undergo further arylation. The quinone **196** is also available by arylation of 2,5-dichloro-1,4-benzoquinone (**192**) with 3,4-dimethoxybenzenediazonium chloride in buffered solution. On treatment with 70% sulfuric acid, the arylquinone **196** affords the dibenzofuran **193** (88%). The cyclization can also be effected photochemically.^{155,156} The arylquinones available by treatment of 2,5- and 2,6-dichloro-1,4-benzoquinones with buffered solutions of diazotized 4-methoxy-3-methyl- and 3-methoxy-4-methylaniline have been cyclized to 2-dibenzofuranols by the agency of aluminum chloride in hot benzene.¹⁵⁷

¹⁵² H.-E. Högberg and P. Komlos, *Acta Chem. Scand., Ser. B* **B33**, 271 (1979).

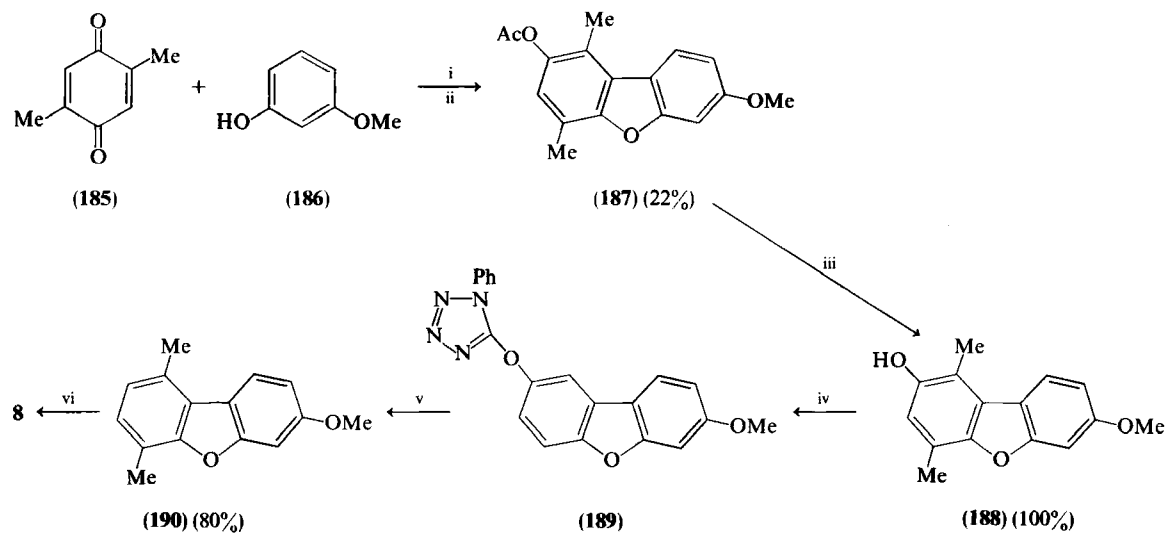
¹⁵³ H.-E. Högberg, *JCS Perkin I*, 2517 (1979).

¹⁵⁴ H.-E. Högberg and H. Hjalmarsson, *Tetrahedron Lett.*, 5215 (1978).

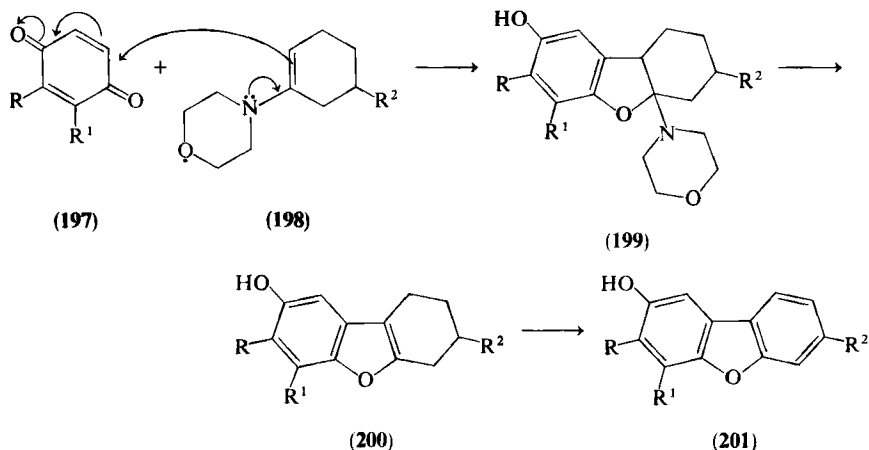
¹⁵⁵ O. C. Musgrave and C. J. Webster, *JCS Perkin I*, 2260 (1974).

¹⁵⁶ H. J. Hageman and W. G. B. Huysmans, *JCS Chem. Commun.*, 837 (1969).

¹⁵⁷ O. C. Musgrave and C. J. Webster, *JCS Perkin I*, 2263 (1974).



SCHEME 48. Reagents: i, H_2SO_4 , AcOH , $\downarrow\uparrow$, 2 h; ii, Ac_2O , py; iii, H^+ , MeOH , $\downarrow\uparrow$, 2 h; iv, 5-chloro-1-phenyltetrazole, K_2CO_3 , DMF , 110°C , 72 h; v, 4 atm, H_2 , EtAc , Pd/C ; vi, MeCOCl , AlCl_3 , 25°C , 6 h.



R	R ¹	R ²	References
H	H	H	158, 159
Me	H	H	160
H	H	Me	160
H	Ph	H	160

SCHEME 50

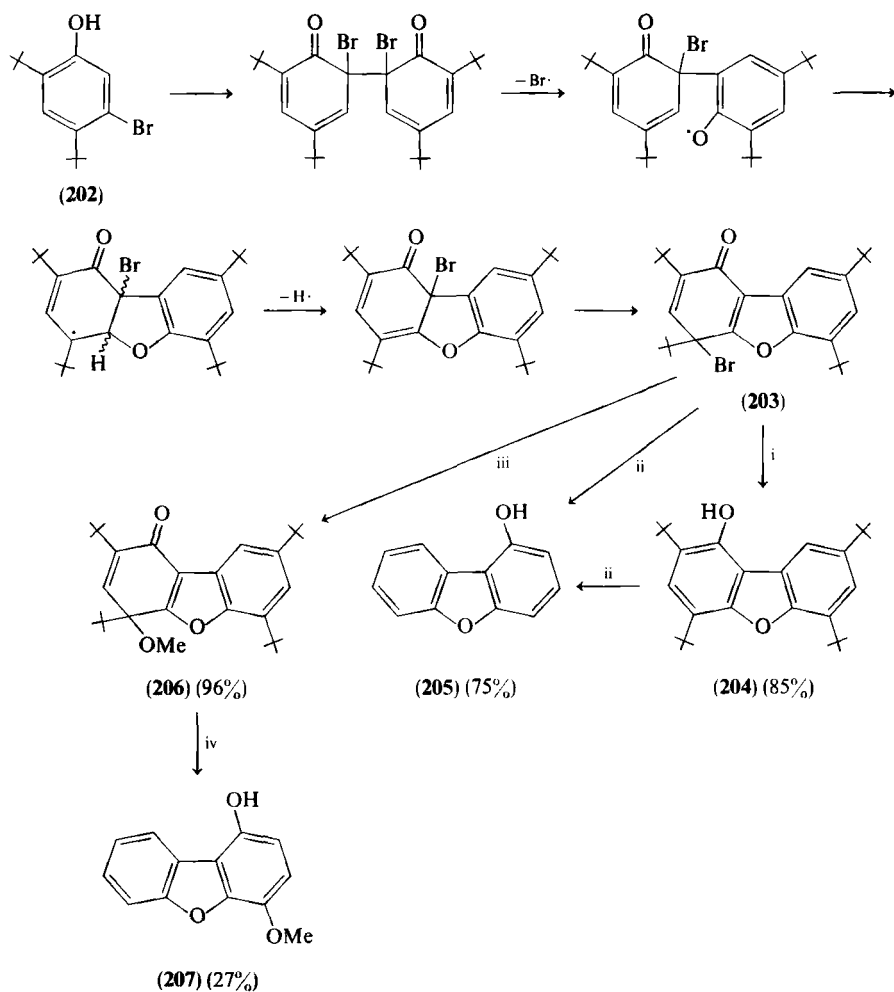
E. OXIDATIVE COUPLING METHODS

1. From Phenols

Oxidative coupling of 2-bromo-4,6-di-*tert*-butylphenol (**202**, Scheme 51) with potassium hexacyanoferrate(III) in a two-phase system consisting of aqueous potassium hydroxide and benzene affords the dibenzofuranone **203** by the mechanism indicated.¹⁶¹ The dibenzofuranone **203** is a convenient source of 1-dibenzofuranol (**205**). On boiling with isopropanol, compound **203** provides the tetra-*tert*-butyl-1-benzofuranol **204**, which may be debutylated by treatment with aluminum chloride in toluene.¹⁶² 1-Dibenzofuranol (**205**) is also obtained by direct treatment of the dibenzofuranone **203** with aluminum chloride in toluene. With boiling methanol, however, compound **203** supplies the methoxy analog **206**, which on mild debutylation affords 4-methoxy-1-dibenzofuranol (**207**).¹⁶¹

¹⁶¹ M. Tashiro, H. Yoshiya, and G. Fukata, *J. Org. Chem.* **46**, 3784 (1981).

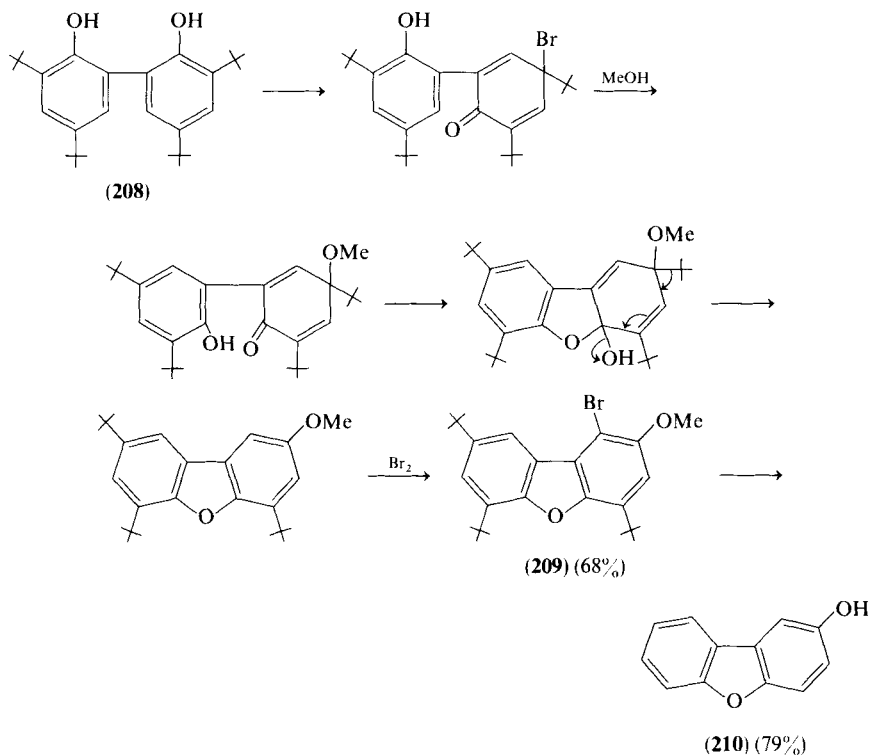
¹⁶² M. Tashiro, H. Yoshiya, and G. Fukata, *Synthesis*, 495 (1980).



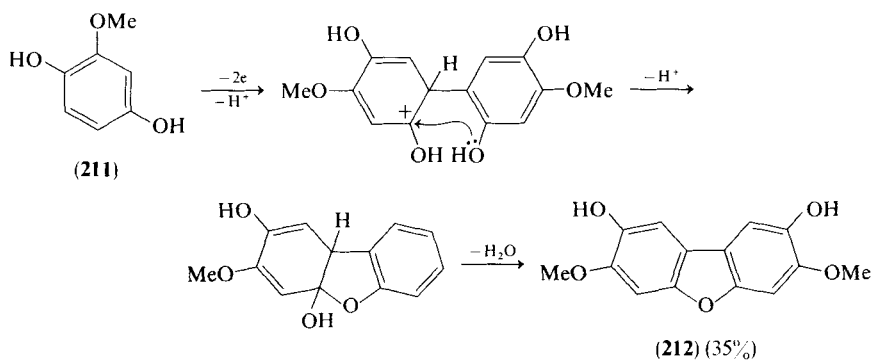
SCHEME 51. Reagents: i, Me_2CHOH , Δ , 5 min; ii, AlCl_3 , PhMe, Δ , 3 h; iii, MeOH, Δ , 5 min; iv, AlCl_3 , PhMe, 25°C , 3 h.

Similar methodology also provides a convenient synthesis of 2-dibenzofuranol.¹⁶³ Treatment of the 2,2'-biphenyldiol **208**, (Scheme 52), readily available by oxidative coupling of 2,4-di-*tert*-butylphenol, with an excess of bromine in methanol affords the 1-bromo-2-methoxydibenzofuran **209**. This undergoes demethylation, debromination, and debutylation on treatment with aluminum chloride in boiling toluene and furnishes 2-dibenzofuranol (**210**).

¹⁶³ M. Tashiro, H. Yoshiya, and G. Fukata, *Heterocycles* **14**, 1955 (1980).



SCHEME 52

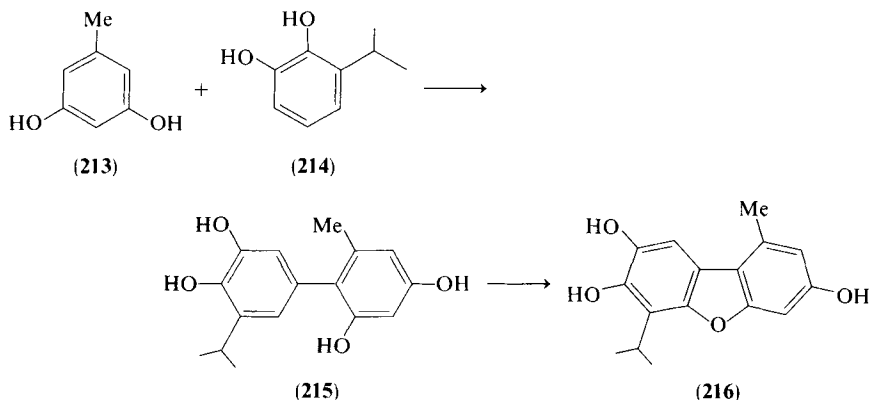


SCHEME 53

2-Methoxyhydroquinone (**211**, Scheme 53) on coupling with iron(III) chloride on silica gel affords the dibenzofurandiols **212**. Electron transfer and C—C coupling para to the methoxy group of the phenoxonium ion inter-

mediate has been evoked to explain this result.¹⁶⁴ The dibenzofurandiol **212** (65%) is also available by electrochemical oxidation of 2-methoxy-1,4-bis(trimethylsilyloxy)benzene.¹⁶⁵

A mixture of orcinol (**213**, Scheme 54) and the catechol **214** on air oxidation in basic solution provides the dibenzofurantriol **216** in unspecified yield. The intermediate **215** can be isolated.¹⁶⁶



SCHEME 54

2. From Oxepinobenzofurans

Sterically hindered phenols containing a *tert*-butyl group at the 2-position and a substituent at position 4, such as a *tert*-butyl,^{69,167,168} a methoxy,^{169,170} a phenoxy,¹⁷¹ or a methyl group,¹⁷² undergo ready oxidative coupling, yielding initially 2,2'-biphenyldiols and then blue solutions of diphenoquinones. These compounds are unstable and undergo valence isomerization to products originally thought to be benzoxets, but in the

¹⁶⁴ T. C. Jemphy, K. A. Z. Gogius, Y. Mazur, and L. L. Miller, *J. Org. Chem.* **46**, 4545 (1981).

¹⁶⁵ R. F. Stewart and L. L. Miller, *J. Am Chem. Soc.* **102**, 4999 (1980).

¹⁶⁶ A. C. Weiss, J. A. Kuhnle, J. J. Windle, and A. K. Wiersema, *Tetrahedron Lett.*, 6251 (1966).

¹⁶⁷ P. Claus, J. S. Gratzl, and K. Kratzl, *Monatsh. Chem.* **103**, 1178 (1972).

¹⁶⁸ V. V. Karpov and M. K. Khidekel, *Zh. Org. Khim.*, **4**, 861 (1968).

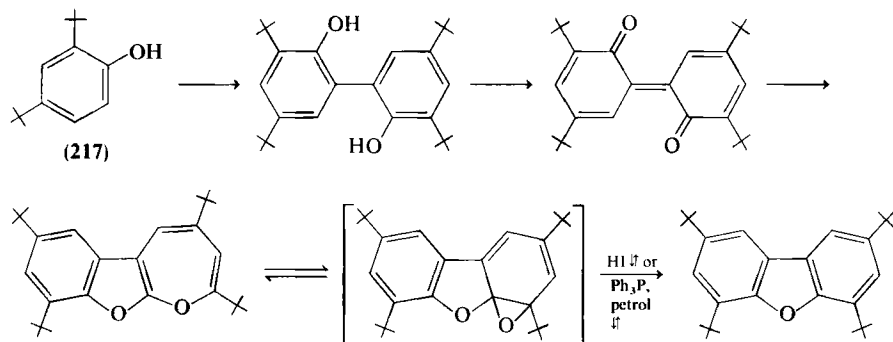
¹⁶⁹ F. R. Hewgill and B. R. Kennedy, *J. Chem. Soc. C*, 362 (1966).

¹⁷⁰ F. R. Hewgill and D. G. Hewitt, *J. Chem. Soc. C*, 726 (1967).

¹⁷¹ D. G. Hewitt, *J. Chem. Soc. C*, 1750 (1971).

¹⁷² F. R. Hewgill and G. B. Howie, *Aust. J. Chem.* **31**, 907 (1978).

light of more recent X-ray studies they are now formulated as oxepino-benzofurans.¹⁷³⁻¹⁷⁵ The oxepinobenzofurans undergo deoxygenation with triphenylphosphine or hydriodic acid, yielding dibenzofurans. The reaction presumably involves oxepin-benzene oxide isomerization. A typical sequence is shown for 2,4-di-*tert*-butylphenol (**217**) in Scheme 55.



SCHEME 55

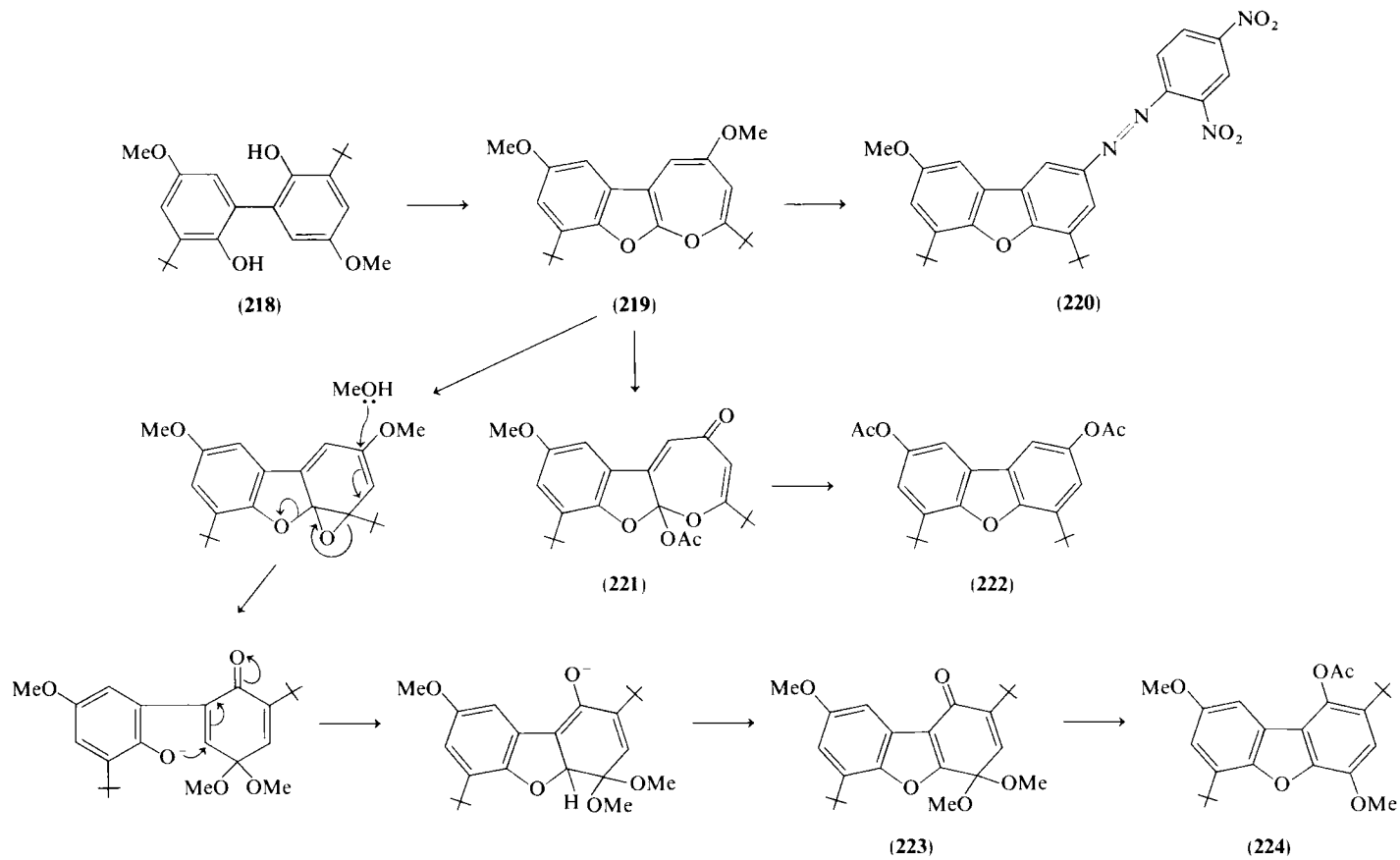
Oxidation of the 2,2'-biphenyldiol (**218**, Scheme 56) by one molar equivalent of lead tetraacetate affords the oxepinobenzofuran **219**. With two molar equivalents of lead tetraacetate the initial product is converted to the acetate **221**, which on reductive acetylation, involving oxepin-benzene oxide isomerization, affords the dibenzofuran **222**.¹⁷⁴ Treatment of the oxepinobenzofuran **219** with ethanolic 2,4-dinitrophenylhydrazine yields the azo compound **220**.¹⁶⁹ On boiling with methanol in air, compound **219** is converted to the dibenzofuranone **223**, again involving valence isomerization.¹⁷⁵ Reductive acetylation then affords the dibenzofuran **224**.¹⁷⁰

Oxidation of 4-methyl-2-*tert*-butylphenol (**225**, Scheme 57) by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol affords the dibenzofuran **228**.¹⁷² The intermediate oxepinobenzofuran **226**, as its valence isomer **227**, undergoes nucleophilic attack by methanol and subsequent dienone-benzene rearrangement with the migration of the methoxy group.

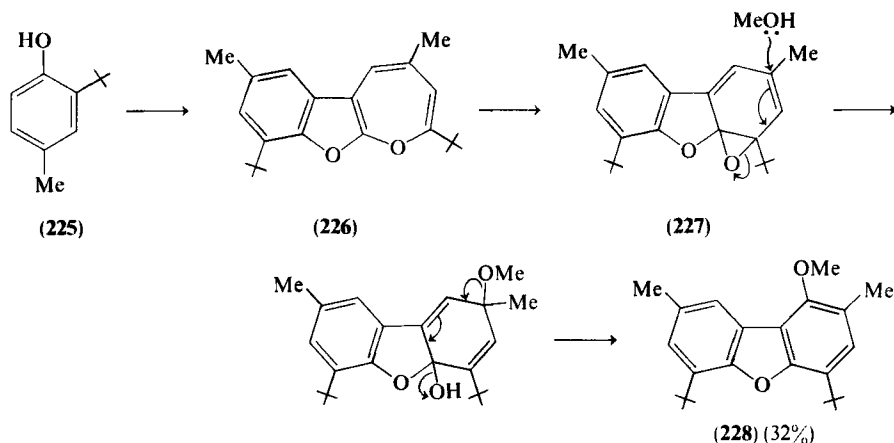
¹⁷³ H. Meier, H.-P. Schneider, A. Rieker, and P. B. Hitchcock, *Angew. Chem., Int. Ed. Engl.* **17**, 121 (1978).

¹⁷⁴ F. R. Hewgill, D. G. Hewitt, G. B. Howie, C. L. Raston, R. J. Webb, and A. H. White, *JCS Perkin I*, 290 (1979).

¹⁷⁵ H.-P. Schneider, W. Winter, and A. Rieker, *J. Chem. Res., Synop.*, 336 (1978).



SCHEME 56

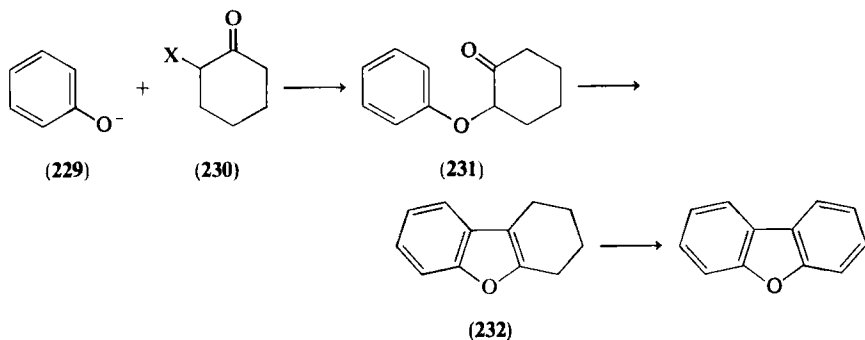


SCHEME 57

F. MISCELLANEOUS METHODS

1. Ebel's Method

Ebel's method is an adaptation of the Stoermer synthesis of benzo-[b]furans and involves the *O*-alkylation of a phenolate anion (**229**, Scheme 58) with a 2-halocyclohexanone (**230**).¹⁷⁶ The resultant 2-phenoxycyclohexanone **231** is then cyclized by polyphosphoric acid, usually at 100°C, or sometimes by concentrated sulfuric acid, to afford a 1,2,3,4-tetrahydrodibenzofuran (**232**). Dehydrogenation to the dibenzofuran is often effected with palladized charcoal,¹⁷⁷ but 2,3-dichloro-5,6-dicyano-1,4-benzoquinone¹⁷⁸



SCHEME 58

¹⁷⁶ F. Ebel, *Helv. Chim. Acta* **12**, 3 (1929).¹⁷⁷ S. Trippett, *J. Chem. Soc.*, 419 (1957).¹⁷⁸ L. M. Berger and R. A. Schmidt, *Ger. Offen*, 2,510,001 [*CA* **84**, 59171 (1976)].

TABLE VI
SYNTHESIS OF DIBENZOFURANS BY EBEL'S METHOD

Halocyclohexanone	Phenol	Dibenzofuran	Overall yield (%)	References
2-Cl	Phenol	Dibenzofuran	—	179
2-Cl	2-OMe	4-OMe	27	176
2-Br-6-Me	Phenol	1-Me	20	177, 180
2-Br	4-Me	2-Me	—	177
2-Br-4-Me	Phenol	3-Me	—	177
2-Br	2-Me	4-Me	—	177
2-Br-5,6-(Me) ₂	Phenol	1,2-(Me) ₂	—	177
2-Br	3,5-(Me) ₂	1,3-(Me) ₂	42	177
2-Br	2,5-(Me) ₂	1,4-(Me) ₂	—	177
2-Br	3,4-(Me) ₂	2,3-(Me) ₂	—	177
2-Br	2,4-(Me) ₂	2,4-(Me) ₂	—	177
2-Br	2,3-(Me) ₂	3,4-(Me) ₂	—	177
2-Cl	2-Ph	4-Ph	29	181, 182
2-Cl	3-CO ₂ Me-2,5-(Me) ₂	3-CO ₂ Me-1,4-(Me) ₂	2	183
2-Br-4-CH ₂ CO ₂ Et	4-Cl	3-CHCO ₂ Et-8-Cl	11	178
2-Br-4-(CH ₂) ₂ CO ₂ Et	4-Cl	3-(CH ₂) ₂ CO ₂ Et-8-Cl	12	178
2-Br-4-CH(Me)CO ₂ Et	4-Cl	3-CH(Me)CO ₂ Et-8-Cl	47	178
2-Br-4-CH(Me)CO ₂ Et	4-Me	3-CH(Me)CO ₂ Et-8-Me	13	178
2-Br-4-CH(Me)CO ₂ Et	4-F	3-CH(Me)CO ₂ Et-8-F	21	178
2-Br-4-CH(Me)CO ₂ Et	4-NHAc	3-CH(Me)CO ₂ Et-8-NH ₂	—	178

¹⁷⁹ F. Winternitz, N. J. Antia, M. Tumilrova, and R. Lachazette, *Bull. Soc. Chim. Fr.*, 1817 (1956).

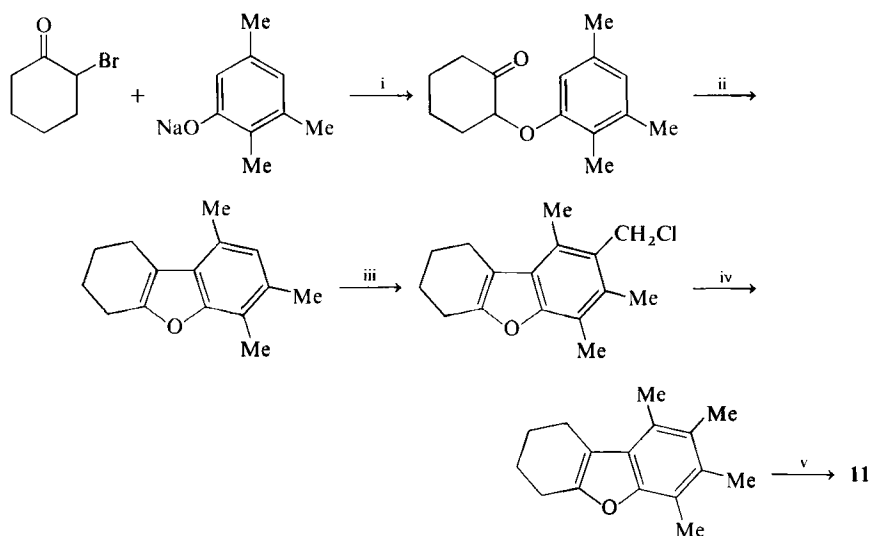
¹⁸⁰ T. Keumi and Y. Oshima, *Fukui Daigashu Kogakubu Kenkyu Hokoku* **24**, 153 (1976) [*CA* **86**, 72324 (1977)].

¹⁸¹ E. B. McCall, A. J. Neale, and T. J. Rawlings, *J. Chem. Soc.*, 4900 (1962).

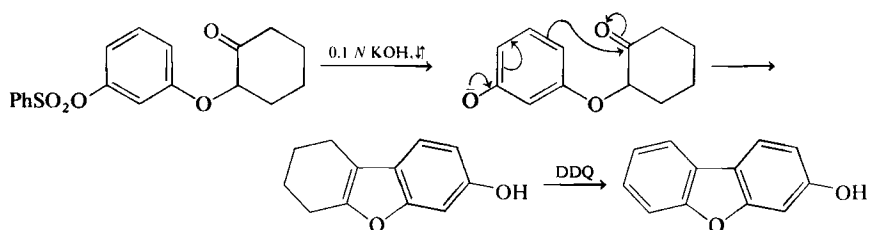
¹⁸² Monsanto Chemicals Ltd., French. Addn. 81, 257 [*CA* **60**, 503 (1964)].

¹⁸³ A. N. Fujiwara, E. M. Acton, and L. Goodman, *J. Heterocycl. Chem.* **6**, 379 (1969).

will also serve. The method finds most use for the synthesis of alkylidibenzofurans. Thus 1,2,3,4-tetramethyldibenzofuran (**11**) was synthesized in 53% overall yield by the method shown in Scheme 59,¹⁷ and other examples are given in Table VI.



SCHEME 59. Reagents: i, PhH, 5 h, 25°C; ii, ppa, 3 h, 100°C; iii, ZnCl₂, HCl, HCHO, 10 h, 75°C; iv, LAH, Et₂O, 41, 2 h; v, 5% Pd/C, 225°C, N₂.



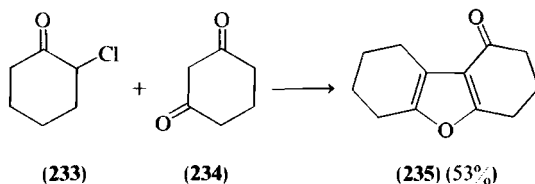
SCHEME 60

MacLeod and Worth have described an interesting adaptation of the Ebel synthesis that depends on an intramolecular aldol condensation initiated by a phenolate anion at the 3'-position of the 2-phenoxy-cyclohexanone and hence provides a synthesis of 3-dibenzofuranols (Scheme 60).¹⁸⁴

¹⁸⁴ J. K. MacLeod and B. R. Worth, *Tetrahedron Lett.*, 237 (1972).

2. Feist–Benary Method

The Feist–Benary synthesis of furans, in which a β -dicarbonyl compound undergoes condensation with an α -haloketone under basic conditions, can be adapted for dibenzofuran synthesis by using cyclohexane derivatives as starting materials. Thus 2-chlorocyclohexanone (**233**, Scheme 61) on reaction with 1,3-cyclohexanedione (**234**) in the presence of aqueous methanolic potassium hydroxide afforded the octahydro-1-dibenzofuranone **235**. This was converted to dibenzofuran by reduction with lithium aluminum hydride and subsequent dehydrogenation with palladized charcoal. Alternatively, reaction with methylmagnesium iodide and subsequent dehydrogenation afforded 1-methyldibenzofuran.¹⁸⁵ Reaction between 5-methyl-1,3-cyclohexanedione and 2-chlorocyclohexanone afforded an octahydro-1-dibenzofuranone, which could be converted to 3-methyl- or 1,3-dimethyldibenzofuran by a similar method.¹⁸⁶ 3-Methyldibenzofuran is also available by condensation of 1,3-cyclohexanedione with 2-bromo-4-methylcyclohexanone and subsequent steps.¹⁸⁷ Reaction between 4-methyl-1,3-cyclohexanedione and 2-chlorocyclohexanone yields a mixture of octahydro-1-dibenzofuranones, which after reduction and dehydrogenation afforded a mixture of 2- and 4-methyldibenzofuran.¹⁸⁶ This method has also been used for the synthesis of phenyldibenzofurans.¹⁸¹



SCHEME 61

3. From Grisadiendiones and Depsidone

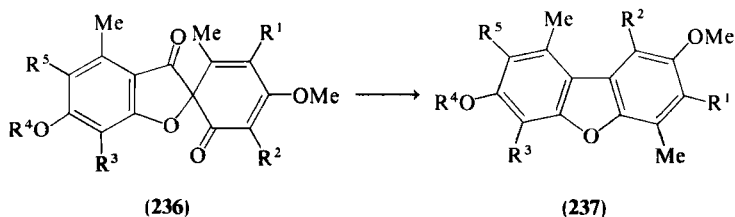
The grisadiendiones (**236**, Scheme 62) on irradiation in benzene through borosilicate glass with light centered at 350 nm yield the dibenzofurans **237**.²⁰ Although the grisadiendiones undergo thermal rearrangement to depsidones,¹⁸⁸ the latter were unchanged under the photochemical conditions.

¹⁸⁵ J. N. Chatterjea and R. R. Ray, *Chem. Ber.* **92**, 998 (1955).

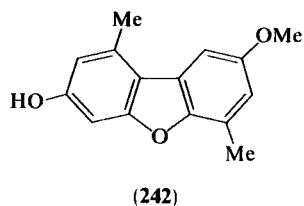
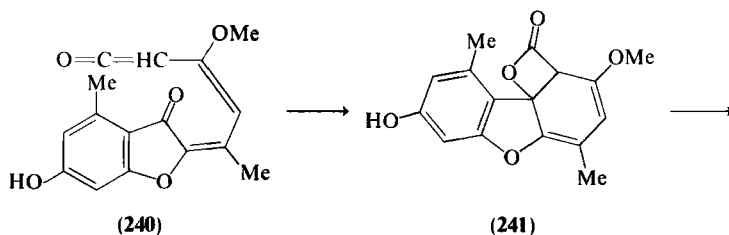
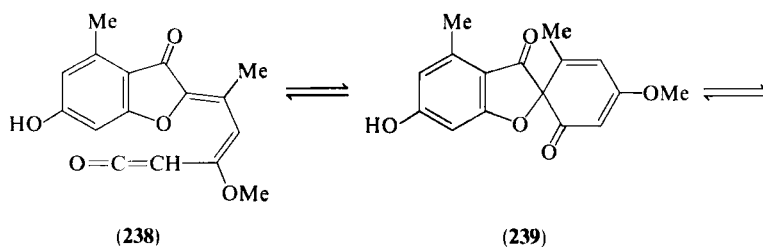
¹⁸⁶ J. N. Chatterjea and V. N. Mehrotra, *J. Indian Chem. Soc.* **39**, 599 (1962).

¹⁸⁷ H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.* **652**, 40 (1962).

¹⁸⁸ T. Sala and M. V. Sargent, *JCS Perkin I*, 855 (1981).



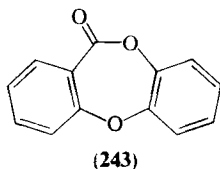
R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)
Cl	Cl	H	H	Cl	59
Cl	Cl	H	Me	Cl	70
Cl	Me	H	H	H	29
Cl	Me	Me	H	H	75
H	H	H	H	H	13



SCHEME 62

The likely mechanism, shown for compound **239**, therefore involves excitation of the dienone chromophore, which results in concerted or radical ring opening to a pair of stereoisomeric dienyketenes (**238** and **240**). Only

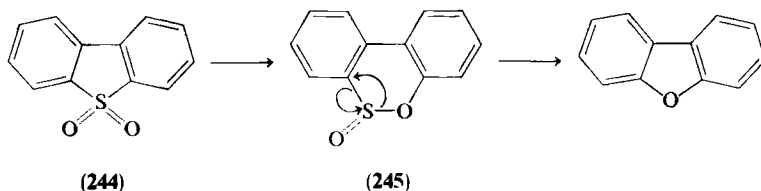
one member (**240**) of the pair is able, because of its stereochemistry, to undergo a thermal $\pi_a + \pi_s$ cyclization, yielding a β -lactone (**241**). Loss of carbon dioxide would then yield the product **242**.



It has been reported that 11*H*-dibenzo[*b,e*][1,4]dioxepin-11-one (depsidone) (**243**) undergoes photochemical decarboxylation and yields dibenzofuran (59%) on irradiation with a high-pressure mercury lamp.¹⁸⁹ The authors do not report whether the irradiation was conducted through silica or borosilicate glass.

4. Pyrolysis of Dibenzothiophene 5,5-Dioxides and Similar Compounds

Flash vacuum pyrolysis of dibenzothiophene 5,5-dioxide (**244**) affords a high yield of dibenzofuran.^{190,191} The sultine **245** (Scheme 63) was postulated as an intermediate, and this has been verified.¹⁹² Octafluorodibenzofuran has been prepared by flash vacuum pyrolysis of the octafluoro analog of compound **244**.¹⁹³ The preparation of dibenzofuran from 2-phenoxybenzenesulfonyl chloride by heating in the presence of a catalyst presumably involves the dioxide **244** as an intermediate.¹⁹⁴



SCHEME 63

¹⁸⁹ S. R. Lele and B. D. Hosangadi, *Indian J. Chem., Sect. B* **16B**, 415 (1978).

¹⁹⁰ E. K. Fields and S. Meyerson, *J. Am. Chem. Soc.* **88**, 2836 (1966).

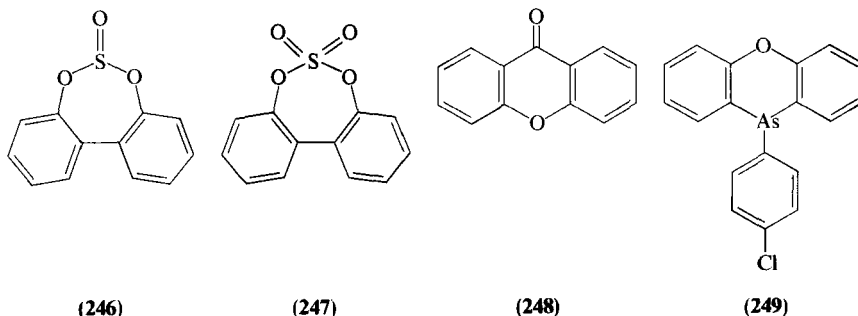
¹⁹¹ W. J. M. van Tilborg and R. Plomp, *Recl. Trav. Chim. Pays-Bas* **96**, 282 (1977).

¹⁹² T. G. Squires, C. G. Vernier, B. A. Hodgson, L. W. Chang, F. A. Davis, and T. W. Panunto, *J. Org. Chem.* **46**, 2373 (1981).

¹⁹³ R. D. Chambers, J. A. Cunningham, and D. J. Spring, *J. Chem. Soc. C*, 1560 (1968).

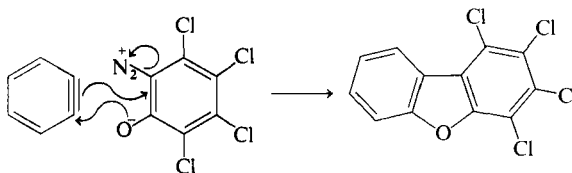
¹⁹⁴ Monsanto Chemicals Ltd., British Patent 1,016,373 [*CA* **64**, 9697 (1966)].

The sulfite **246** and the sulfate **247** produce 1-dibenzofuranol on pyrolysis.¹⁹⁵ Xanthone (**248**)¹⁹⁶ and the phenoxarsine (**249**)¹⁹⁷ are reported to produce dibenzofuran on pyrolysis. The pyrolysis of a mixture of nitrobenzene and benzene also produces some dibenzofuran.¹⁹⁸



5. From Benzene-2-diazo 1-Oxides and Benzyne

When benzyne is generated by aprotic diazotization of anthranilic acid in boiling 1,2-dimethoxyethane in the presence of substituted benzene-2-diazo 1-oxides (*o*-quinonediazides), dibenzofurans are obtained in moderate yields (Scheme 64).¹⁹⁹



SCHEME 64

6. Industrial Methods

Phenol and alkyl-substituted phenols yield dibenzofuran and alkyl dibenzofurans by catalytic dehydration-dehydrogenation over thorium or cerium oxides.²⁰⁰⁻²⁰² This reaction can also be achieved by thermal cracking of

¹⁹⁵ D. C. De Jongh and R. Y. van Fossen, *J. Org. Chem.* **37**, 1129 (1972).

¹⁹⁶ N. A. Orlov and W. W. Tistschenko, *Ber. Dtsch. Chem. Ges.* **63**, 2948 (1930).

¹⁹⁷ J. C. Tou, C.-S. Wang, and E. G. Alley, *Org. Mass Spectrom.* **3**, 747 (1970).

¹⁹⁸ E. K. Fields and S. Meyerson, *J. Am. Chem. Soc.* **89**, 3224 (1967).

¹⁹⁹ W. Ried and J. T. S. Eng, *Justus Liebigs Ann. Chem.* **727**, 219 (1969).

²⁰⁰ N. A. Fishel and D. E. Gross, U.S. Patent 4,035,428 [CA **87**, 134589 (1977)].

²⁰¹ N. A. Fishel and D. E. Gross, U. S. Patent 4,008,254 [CA **86**, 171247 (1977)].

²⁰² N. A. Fishel, U.S. Patent 4,013,694 [CA **87**, 23029 (1977)].

phenols at short contact time at atmospheric pressure. The reaction mechanism has been studied²⁰³ and the subject has been reviewed.⁷ Vapor-phase oxidation of phenol by oxygen at 630–650°C also produces dibenzofuran.²⁰⁴

The pyrolysis of 2-biphenylol produces dibenzofuran.²⁰⁵ The reaction has been catalyzed by palladium,²⁰⁶ or a mixture of platinum and palladium on charcoal.²⁰⁷ The conversion was as high as 75% at 400–500°C.²⁰⁷ The reaction has also been carried out in a glow discharge.²⁰⁸ Dehydrogenation of 2-cyclohexylphenol also produces dibenzofuran in low yield.²⁰⁹

Cyclohexanone can be converted to 2-cyclohex-1-enylcyclohexanone by exposure to Amberlyst 15H, and this compound undergoes oxidative dehydrocyclization, yielding dibenzofuran (63%) on passage over a mixed-oxide catalyst.^{210,211}

Diphenyl ether may be dehydrogenated to dibenzofuran by passage over 5% palladized charcoal at 450–550°C.²¹²

IV. Reactions of Dibenzofuran

A. ELECTROPHILIC SUBSTITUTION

The partial rate factors for dibenzofuran relative to a benzene position, for protodetrition,²¹³ protodetrimethylsilylation,²¹⁴ nitration with nitric acid in acetic anhydride,²¹⁵ and benzoylation²¹⁶ with benzoyl chloride and aluminum chloride in nitrobenzene at 15°C are shown in Table VII along with the relevant values for diphenyl ether. It is seen that by introducing the biphenyl bond in diphenyl ether the reactivity is lowered at both the positions ortho (4-) and para (2-) to the oxygen of dibenzofuran. This lowering of reactivity has been attributed to the fact that the 2- and 4-positions, as

²⁰³ R. Cypres and B. Bettens, *Tetrahedron* **30**, 1253 (1974).

²⁰⁴ I. I. Ioffe, *Zh. Fiz. Khim.* **28**, 772 (1954) [*CA* **49**, 6697 (1955)].

²⁰⁵ W. J. Hale and W. C. Stroesser, U.S. Patent 1,808,349 [*CA* **25**, 4286 (1931)].

²⁰⁶ M. Orchin, *J. Am. Chem. Soc.* **70**, 495 (1948).

²⁰⁷ H. Yasui and H. Suzumura, *Aromatikkusu* **30**, 293 (1978) [*CA* **91**, 5057 (1979)].

²⁰⁸ H. Suhr and R. I. Weiss, *Justus Liebigs Ann. Chem.*, 496 (1976).

²⁰⁹ H. Matsumura, K. Imafuku, I. Takano, and S. Matsuura, *Bull. Chem. Soc. Jpn.* **44**, 567 (1971).

²¹⁰ P. A. Moggi and G. Iori, Swiss Patent 619,943 [*CA* **92**, 192120 (1980)].

²¹¹ P. A. Moggi and G. Iori, Ger. Offen. 2,552,652 [*CA* **85**, 108512 (1976)].

²¹² Imperial Chemical Industries Ltd., British Patent 929,376 [*CA* **59**, 12762 (1963)].

²¹³ R. Baker and C. Eaborn, *J. Chem. Soc.*, 5077 (1961).

²¹⁴ C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961).

²¹⁵ M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.* 3079 (1968).

²¹⁶ T. Keumi, S. Shimakawa, and Y. Oshima, *Nippon Kagaku Kaishi*, 1518 (1977) [*CA* **88**, 36840 (1978)].

TABLE VII
PARTIAL RATE FACTORS FOR ELECTROPHILIC SUBSTITUTION OF DIBENZOFURAN
AND DIPHENYL ETHER

Reaction	Partial Rate Factors					
	Dibenzofuran Position				Diphenyl Ether Position	
	1	2	3	4	ortho	para
Protodetrithiation	135	3670	313	160	6930	30,000
Protodesilylation	0.65	19.2	2.4	0.92	8.7	88.5
Nitration	47	94	94	19.8	117	234
Benzoylation	34.6	4520	371	—	—	—

well as being para and ortho to the heteroatom, are also meta to a substituted phenyl group that may deactivate these positions. The major factor responsible for the lowering of reactivity, however, is ascribed to the oxygen lone pair being involved in resonance and thus imparting aromatic character to the five-membered ring.²¹⁴ It has been pointed out that there is a marked difference in reactivity at the 2- and 4-positions of dibenzofuran compared with the para and ortho positions of diphenyl ether.²¹⁷ A similar difference in the reactivity of the α and β positions of indane was observed many years ago and is known as the Mills–Nixon effect.²¹⁸

A similar origin of this effect has been postulated for both cases.^{217,218} For the case of dibenzofuran, the transition state leading to 4-substitution will possess a 4a–9b bond that has higher double-bond character than in the ground state, thus leading to increased strain in the five-membered ring. This transition state will therefore be destabilized. Conversely, the transition state for 2-substitution will possess a 4a–9b bond that has less double-bond character than in the ground state, so that this transition state will be stabilized and reactivity will be increased at the 2-position. The reactivity at the 4-position will therefore be less, and at the 2-position will be greater than predicted on the basis of the reactivity of diphenyl ether. The low reactivity of the 1- and 4-positions has also been attributed to steric hindrance by H-9 and by the lone-pair orbital on oxygen.²¹⁶

The 2-position of dibenzofuran represents an average of 88% of the total reactivity of dibenzofuran for protodetrithiation, protodetrithymethylsilylation, and benzoylation, which accords well with the results recorded for other electrophilic substitution reactions of dibenzofuran. Mercuration and lithia-

²¹⁷ R. Taylor, *J. Chem. Soc. B*, 1559 (1968).

²¹⁸ J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron* **21**, 1665 (1965).

tion appear anomalous, but these reactions are presumably directed by the coordinating power of the oxygen atom. The values for nitration also appear to be anomalous, and no convincing explanation can readily be offered. It has been suggested that the nitration reaction is mechanistically complex.²¹⁹

The latest results on the nitration of dibenzofuran²²⁰ are qualitatively in agreement with those of Dewar and Urch.^{215,221} In acetic acid, nitration with nitric acid at low conversion gave the 1-nitro (10%), 2-nitro (26%), 3-nitro (62%), and the 4-nitro isomer (2%). However, with nitric acid in trifluoroacetic acid at 0°C, the isomer distribution was: 1-nitro (4%), 2-nitro (6%), 3-nitro (90%), and 4-nitro isomer (trace). The 3-nitro isomer can be isolated in 80% yield under these conditions. With alkyl nitrates in nitromethane in the presence of aluminum chloride the predominant product is the 2-nitro isomer. Thus under these conditions nitration with 1-cyano-1-methylethyl nitrate gave 92% mononitrodibenzofurans with the following isomer distribution: 1-nitro (11%), 2-nitro (51%), 3-nitro (36%), and 4-nitro (2%). On a preparative scale, nitration of dibenzofuran with ethyl nitrate and aluminum chloride at 25°C for 1 h gave an 80% yield of mononitrodibenzofurans from which the 2-nitro isomer was isolated in 28% yield by chromatography.

The acylation of dibenzofuran is carried out under the usual Friedel-Crafts conditions with an acid chloride or an acid anhydride in the presence of aluminum chloride. Dibenzofuran on treatment with 2-trifluoromethanesulfonyloxypyridine and benzoic acid in boiling trifluoroacetic acid produces the 2-benzoyl derivative in 75% yield. The species responsible for benzoylation is probably a mixed anhydride of trifluoromethanesulfonic acid and benzoic acid.²²² Dibenzofuran on treatment with 2-benzoyloxypyridine and trifluoroacetic acid also produces the 2-benzoyl compound (21%).²²³ The kinetics of the acetylation of dibenzofuran with acetyl chloride and aluminum chloride in nitroethane at 25°C have been studied.²²⁴ Only the 2-acetyl compound was detected by the methods used. The rate obtained is in general agreement with the studies mentioned previously. The rate of acetylation of diphenyl ether relative to toluene was 138 (± 16), whereas that of dibenzofuran was 5.9 (± 0.3). In contrast, the benzoylation of dibenzofuran with benzoyl chloride in the presence of aluminum chloride in nitrobenzene at

²¹⁹ J. H. Ridd, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 4, p. 101. Academic Press, New York, 1971.

²²⁰ T. Keumi, H. Yamada, H. Takahashi, and H. Kitajima, *Bull. Chem. Soc. Jpn.* **55**, 629 (1982).

²²¹ M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957).

²²² T. Keumi, H. Saga, R. Taniguchi, and H. Kitajima, *Chem. Lett.*, 1099 (1977).

²²³ T. Keumi, R. Taniguchi, and H. Kitajima, *Synthesis*, 139 (1980).

²²⁴ P. Finocchiaro, *Ann. Chim. (Rome)* **58**, 647, 787 (1969).

15°C produced 93.3% of benzoylated products with the following distribution: 1- (0.6%), 2- (90.5%), 3- (8.7%), and 4-isomer (0.2%).²²⁵ The amount of 3-isomer was higher at higher temperatures or in chlorinated hydrocarbon solvents. Friedel–Crafts acylation of dibenzofuran has been carried out with a large range of aliphatic^{226–228} and aromatic^{229–233} acid chlorides. Acetic anhydride,²³⁴ succinic anhydride,²³⁵ and phthalic anhydride²³⁶ have also been used as acylating agents. In general, the 2-substituted products are obtained in good yields accompanied by varying amounts of the 3-isomers or the 2,8-disubstituted compounds.

A carboxylic acid group may be introduced into the 2-position of dibenzofuran by Friedel–Crafts reaction with 2,2-dichloro-1,3-benzodioxole (catechol dichloromethylene ether) and hydrolysis of the resultant ester.²³⁷ Similarly, reaction with methylphenylcarbamoyl chloride produces the 2-(*N*-methyl-*N*-phenylcarboxamide) or the 2,8-disubstituted derivative under more stringent conditions. Controlled reduction of these amides with lithium aluminum hydride supplies the corresponding aldehydes.²³⁸

Chloromethylation of dibenzofuran with paraformaldehyde in the presence of hydrogen chloride can be controlled to produce either the 2-chloromethyl^{239,240} or the 2,8-bis(chloromethyl) compound.²⁴¹ Phosphoric acid

²²⁵ T. Keumi, S. Shimakawa, and Y. Oshima, *Nippon Kagaku Kaishi*, 1518 (1977) [*CA* **88**, 36840 (1978)].

²²⁶ N. P. Buu-Hoi and R. Royer, *Recl. Trav. Chim. Pays-Bas* **67**, 175 (1948).

²²⁷ N. P. Buu-Hoi and R. Royer, *Recl. Trav. Chim. Pays-Bas* **69**, 861 (1950).

²²⁸ W. M. Whaley and C. White, *J. Org. Chem.* **18**, 309 (1953).

²²⁹ R. G. Johnson, H. B. Willis, and H. Gilman, *J. Am. Chem. Soc.* **76**, 6407 (1954).

²³⁰ K. Hofer and R. Kessler, French Patent 1,531,950 [*CA* **71**, 30359 (1969)].

²³¹ T. Keumi, S. Suzuki, S. Yamada, O. Mamoru, and Y. Oshima, *Kogyo Kagaku Zasshi* **73**, 2417 (1970) [*CA* **75**, 20076 (1971)].

²³² T. Keumi, K. Kitagawa, and Y. Oshima, *Kogyo Kagaku Zasshi* **73**, 536 (1970) [*CA* **73**, 45232 (1970)].

²³³ T. Keumi, Y. Maegawa, T. Takegami, and Y. Oshima, *Nippon Kagaku Kaishi*, 1505 (1973) [*CA* **79**, 136927 (1973)].

²³⁴ M. I. Dovgosheya and B. M. Krasovitski, *Zh. Org. Khim.* **2**, 1288 (1966) [*CA* **66**, 55124 (1967)].

²³⁵ G. Schilling and T. A. Dobson, Ger. Offen. 2,314,869 [*CA* **81**, 25527 (1974)].

²³⁶ T. Keumi, S. Shimakawa, and Y. Oshia, *Nippon Kagaku Kaishi*, 216 (1975) [*CA* **83**, 9655 (1975)].

²³⁷ G. Vasilin, A. Gioba, and O. Maior, *An. Univ. Bucuresti, Ser. Stiint Nat., Chim.* **16**, 57 (1967) [*CA* **71**, 3339 (1969)].

²³⁸ F. Weygand and R. Mitgau, *Chem. Ber* **88**, 301 (1955).

²³⁹ R. G. Johnson, H. B. Willis, G. A. Martin, W. H. Kirkpatrick, J. Swiss, and H. Gilman, *J. Org. Chem.* **21**, 457 (1956).

²⁴⁰ Miles Laboratories Inc., British Patent 703,257 [*CA* **49**, 5531 (1955)].

²⁴¹ M. S. Ogii, V. I. Shcherbachenko, S. N. Petrunyan, N. K. Moshchinskaya, *Vopr. Khim. Khim. Tekhnol.*, 87 (1972) [*CA* **78**, 84153 (1973)].

or zinc chloride are used as catalysts. Dibenzofuran fails to undergo formylation under the Vilsmeier–Haack conditions²⁴² but affords the 2-aldehyde in 40% yield under the Gattermann conditions or in 58% yield on treatment with dichloromethyl methyl ether and tin(IV) chloride.²⁴³

Dibenzofuran undergoes Friedel–Crafts alkylation with alkyl halides^{244,245} or alkenes^{246,247} in the presence of Lewis acids. The products are the 2-substituted or the 2,8-disubstituted compounds. Sulfonation of dibenzofuran can be achieved with sulfuric acid at 100°C for 1 h, producing the 2-sulfonic acid in 75% yield. Longer reaction times increase the amount of 2,8-disulfonic acid.²⁴⁸ Reaction with chlorosulfonic acid can be achieved under similar conditions.²⁴⁹

Halogenation of dibenzofuran produces the 2-halo compounds. Bromination can be achieved in good yield with bromine in acetic acid²¹⁴ or with *N*-bromosuccinimide in boiling carbon tetrachloride.²²⁶ The 2,8-dibromo compound has been made, using dioxane dibromide.²⁵⁰ Chlorination of dibenzofuran in acetic acid in the presence of iron powder can be controlled to yield the 2-chloro or the 2,8-dichloro compounds.²⁵¹ 2-Chlorodibenzofuran is best prepared by reaction of dibenzofuran with phosphorus pentachloride.²⁵² 2-Iododibenzofuran (45%) results from treatment of dibenzofuran with iodine in boiling chloroform in the presence of nitric acid.²⁵³ 2,8-Diododibenzofuran is best prepared by reaction of dibenzofuran with iodine and iodic acid in aqueous acetic acid.⁹²

When an electron-withdrawing group is present in any position of one benzenoid ring of dibenzofuran, then the electrophile usually attacks the other benzenoid ring at the 8-position. Nitration usually occurs, however, at the 7-position. When there is an alkyl group at the 2-position, acylation occurs predominantly at the 8-position, but when there is a methyl group

²⁴² J. N. Chatterjea, *J. Indian Chem. Soc.* **34**, 347 (1957).

²⁴³ B. C. Elmes and J. M. Swan, *Aust. J. Chem.* **22**, 1963 (1969).

²⁴⁴ R. K. Abbott, U.S. Patent 2,500,732 [*CA* **44**, 5390 (1950)].

²⁴⁵ Monsanto Chemicals Ltd., French Patent 1,351,472 [*CA* **61**, 9468 (1964)].

²⁴⁶ Rütgerswerke A.-G., British Patent 760,986 [*CA* **51**, 15589 (1957)].

²⁴⁷ O. G. Akperov and M. N. Agopyan, *Uch. Zap. Azerb. Gos. Univ., Ser. Khim. Nauk*, **64** (1972) [*CA* **78**, 147711 (1973)].

²⁴⁸ R. Wendland, C. H. Smith, and R. Muraca, *J. Am. Chem. Soc.* **71**, 1593 (1949).

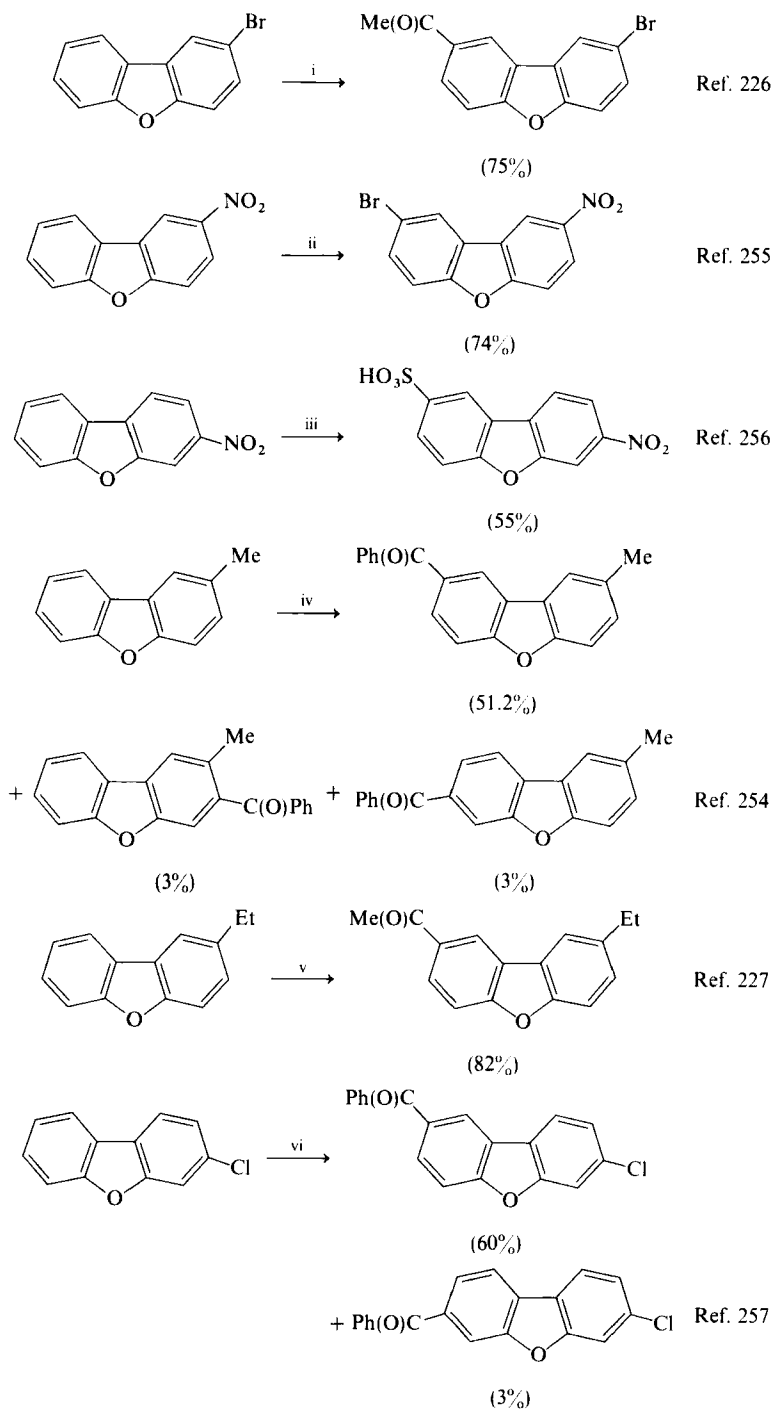
²⁴⁹ Yu. A. Moskuichev, V. A. Sapunov, and G. S. Mironov, *Zh. Prikl. Khim. (Leningrad)* **53**, 1619 (1980) [*CA* **94**, 30296 (1981)].

²⁵⁰ Y. Oshima, T. Keumi, K. Miyata, T. Yamaguchi, and T. Sawa, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **16**, 237 (1968) [*CA* **71**, 112712 (1969)].

²⁵¹ K. Oita, R. G. Johnson, and H. Gilman, *J. Org. Chem.* **20**, 657 (1955).

²⁵² F. C. Whitmore and D. P. Langlois, *J. Am. Chem. Soc.* **55**, 1518 (1933).

²⁵³ H. Gilman, G. E. Brown, W. G. Bywater, and W. H. Kirkpatrick, *J. Am. Chem. Soc.* **56**, 2473 (1934).



SCHEME 65: Reagents: i, MeCOCl, AlCl₃, CS₂, 25°C, 67 h; ii, Br₂, AcOH ↓, 6 h; iii, H₂SO₄, 100°C, 30 min; iv, PhCOCl, PhNO₂, AlCl₃, 20°C, 1 h; v, MeCOCl, AlCl₃, PhH, 25°C, 5 d; vi, PhCOCl, AlCl₃, PhNO₂, 50–60°C.

at the 3-position, acylation occurs predominantly at the 2-position.²⁵⁴ Examples are quoted by Parham,¹ and others are shown in Scheme 65.

Strong electron-releasing substituents, such as hydroxy, methoxy, or acetylamino groups, generally promote electrophilic substitution in the same ring. The electrophilic substitution of dibenzofurans with such a 1-substituent has been little studied. Bromination of 1-dibenzofuranol affords a monobromo compound of unknown structure.⁶³ Bromination of 2-dibenzofuranol affords the 1-bromo compound (43%) and some of the 3-bromo isomer.⁶³ Nitration of 2-dibenzofuranol similarly affords the 1- and 3-nitro compounds in the ratio 4:1.⁹¹ Fries rearrangement of 2-acetyldibenzofuran at 140°C with aluminum chloride also yields predominantly 1-acetyl-2-dibenzofuranol (~48%) and some of the 3-isomer (20%).²⁵⁸ The Mannich reaction of 2-dibenzofuranol affords only 1-dimethylamino-2-dibenzofuranol²⁵⁹; likewise, coupling with benzenediazonium chloride proceeds only at the 1-position.²⁶⁰ By contrast, electrophilic substitution of 2-methoxydibenzofuran affords predominantly the 3-substituted derivatives. Bromination provides the 3-bromo compound (33%) and some of the 1-bromo isomer,⁶³ and nitration yields the 3-nitro compound (81%) and the 1-nitro isomer (8%).⁹¹ Acetylation of 2-methoxydibenzofuran with acetyl chloride and aluminum chloride in nitrobenzene at 25°C gives exclusively the 3-acetyl compound,^{261,262} but benzoylation under similar conditions yields a mixture of the 1- and 3-benzoyl isomers.²⁶² Vilsmeier–Haack formylation yields only the 3-aldehyde.²⁶¹ Bromination and nitration of 2-acetylaminodibenzofuran occur at the 3-position,¹ but bromination of the 2-amino compound proceeds only at the 1-position.²⁵⁸

As expected, electrophilic substitution of a compound with a powerful electron-releasing substituent at the 3-position results in the 2-substituted compound. Thus bromination and diazonium coupling of 3-dibenzofuranol occurs at the 2-position,¹ and bromination,¹ chlorination,²⁶³ and nitration²⁶⁴

²⁵⁴ T. Keumi, H. Hashio, Y. Maegawa, and Y. Oshima, *Nippon Kagaku Kaishi*, 1708 (1974) [CA 82, 43114 (1975)].

²⁵⁵ H. Gilman and R. K. Ingham, *J. Am. Chem. Soc.* 75, 4843 (1953).

²⁵⁶ R. J. Wendland, J. Rode, and R. Meintzer, *J. Am. Chem. Soc.* 75, 3606 (1953).

²⁵⁷ K. Takashi, S. Yamada, H. Noda, and Y. Oshima, *Nippon Kagaku Kaishi*, 387 (1972) [CA 76, 126689 (1972)].

²⁵⁸ H. Gilman, T. H. Cook, J. A. Hogg, J. Swiss, and R. G. Johnson, *J. Am. Chem. Soc.* 76, 5783 (1954).

²⁵⁹ H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.* 70, 3963 (1948).

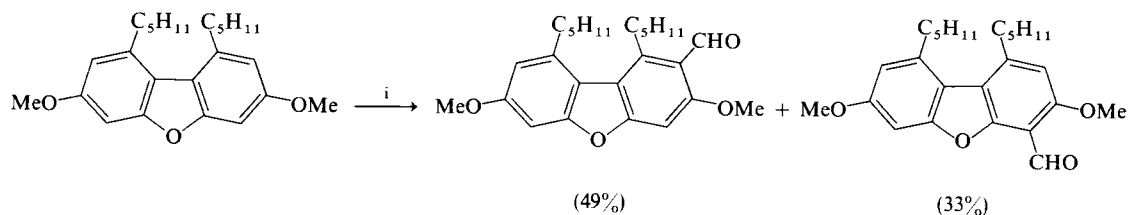
²⁶⁰ H. Gilman and M. W. Van Ess, *J. Am. Chem. Soc.* 61, 3146 (1939).

²⁶¹ C. Routier, N. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 4276 (1956).

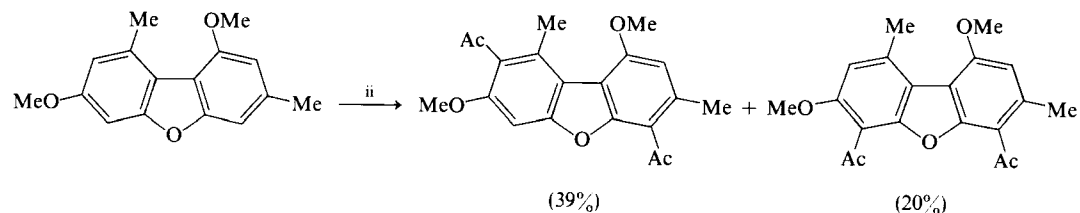
²⁶² T. Keumi, S. Yamada, and Y. Oshima, *Nippon Kagaku Kaishi*, 1438 (1972) [CA 77, 151769 (1972)].

²⁶³ S. Shibata, S. Natori, and T. Kawakami, *Pharm. Bull.* 2, 45 (1954) [CA 50, 294 (1956)].

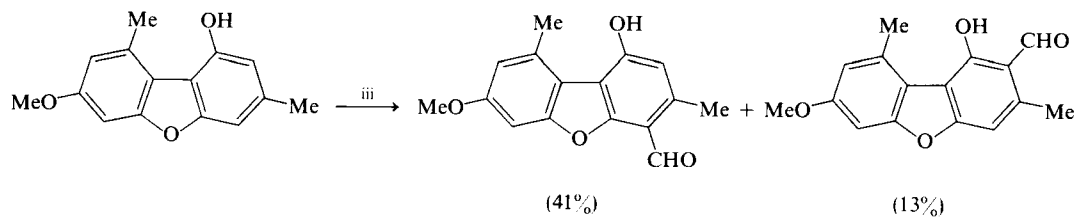
²⁶⁴ W. Lagenbeck, K. Rühlmann, H. H. Reif, and F. Stolze, *J. Prakt. Chem.* [4] 4, 136 (1956) [CA 51, 12065 (1957)].



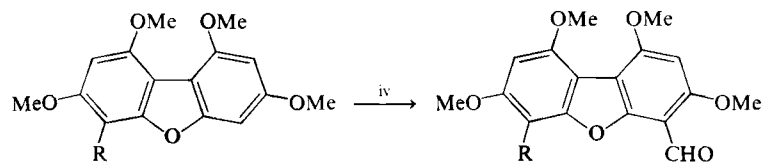
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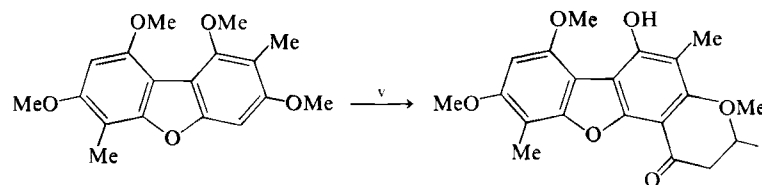


Ref. 23



R = H (91%)
R = Me (97%)

Ref. 12



Ref. 12, 22

SCHEME 66. Reagents: i, Cl_2CHOMe , TiCl_4 , CH_2Cl_2 , -10°C , 1 h; MeCOCl , SnCl_4 , PhH , 25°C , 16 h; iii, PhMeNCHO , POCl_3 , 25°C , 3 h; iv, DMF , POCl_3 , 25°C , 1 h; v, $\text{Me}_2\text{CHCH}_2\text{COCl}$, SnCl_4 , CH_2Cl_2 , 25°C , 65 h.

occur at the 2-position. Vilsmeier-Haack formylation of 3-(dimethylamino)-dibenzofuran results in the 2-aldehyde and some of the 4-aldehyde.²⁶⁵

When there is an electron-releasing substituent in the 4-position, the electrophile attacks the 1-position. This has been used as a convenient way of preparing 1-substituted dibenzofurans by removal of an amino group at the 4-position. Bromination,⁶³ chlorination,²⁶⁶ and diazo coupling²⁶⁰ of 4-dibenzofuranol occur at the 1-position. Bromination⁶³ and Vilsmeier-Haack formylation²⁶⁷ of 4-methoxydibenzofuran provide the 1-substituted derivatives. Nitration and bromination of 4-acetylaminodibenzofuran take a similar course.¹

Few data are available on the electrophilic substitution of dibenzofurans containing more than one substituent. 1,4-Dimethyldibenzofuran affords, as expected, the 2-aldehyde on reaction with dichloromethyl methyl ether and tin(IV) chloride.²⁴³ The nitration of 2,4-dimethyldibenzofuran has also been studied.⁵⁸ Acetylation of 4-methoxy-7-nitro- and 8-nitrodibenzofuran occurs exclusively at the 1-position.²⁶⁸ Similarly, both 4,6- and 3,4-dimethoxydibenzofuran undergo bromination and acetylation at the 1-position.²⁶⁹ The acetylation of 1,3-dimethyl-,¹³ 1,4-dimethyl-,^{118,133,154} and 2,4-dimethyl-7-methoxydibenzofuran¹³ have been studied; the acetyl group enters the 8-position. The chlorination of 3,7-dichlorodibenzofuran has also been studied.²⁵

The electrophilic substitution of some polysubstituted dibenzofurans is shown in Scheme 66.

B. NUCLEOPHILIC SUBSTITUTION

Bromo- and iododibenzofurans have been converted to the amino-compounds by reaction with ammonia,^{61,250,271} or to phenols by reaction with hydroxide,^{63,92} both in the presence of copper catalysts at high temperatures and pressures. Thus 2-iododibenzofuran is converted to the 2-amino compound (95%) with ammonia in the presence of copper(I) bromide at 200–210°C for 24 h,²⁷¹ and 2-bromodibenzofuran affords the corresponding phenol (56–75%) on treatment with aqueous sodium hydroxide in the presence of copper and copper(II) sulfate at 240°C for 12 h.⁶³

²⁶⁵ V. Farcasan and I. Cristea, *Rev. Roum. Chim.* **18**, 469 (1973) [*CA* **79**, 5195 (1973)].

²⁶⁶ H. Gilman and D. L. Esmay, *J. Am. Chem. Soc.* **76**, 5787 (1954).

²⁶⁷ H. Gilman, S. Avakian, J. A. Hogg, and R. G. Johnson, *J. Am. Chem. Soc.* **75**, 6310 (1953).

²⁶⁸ S. O. Onyiriuka and A. H. Rees, *J. Chem. Soc. C*, 504 (1966).

²⁶⁹ H. Gilman and L. C. Cheney, *J. Am. Chem. Soc.* **61**, 3149 (1939).

²⁷⁰ J. A. Elix, *Aust. J. Chem.* **25**, 1129 (1972).

²⁷¹ E. V. Brown and R. L. Coleman, *Org. Prep. Proced. Int.* **5**, 125 (1973).

Nitriles are available by treatment of bromodibenzofurans with copper(I) cyanide in boiling quinoline or *N,N*-dimethylformamide.^{61,272} Halodibenzofurans also undergo Ullmann coupling with potassium phenolates.²⁷³ 4-Dibenzofuranol²⁷⁴ and 4,6-dibenzofurandiol²⁶⁹ undergo the Bucherer reaction and afford the corresponding amines.

When 4-bromo- or 4-iododibenzofuran is treated with sodamide or a lithium dialkylamide, cine substitution occurs and the 3-amino derivative results.^{239,275} The 4,6-diiodo derivative similarly gives the 3,7-diamino compound.²⁷⁵

1,2,3,4-Tetrafluorodibenzofuran is attacked by nucleophiles exclusively at the 3-position⁹⁴; similarly octafluorodibenzofuran is attacked at the 3- and 7-positions.¹⁹³

C. HOMOLYTIC SUBSTITUTION

Homolytic substitution has been little studied, and work has been confined to the reaction of dibenzofuran with carboxymethyl radicals produced from acetyl peroxide or di-*tert*-butyl peroxide in boiling acetic acid or by pyrolysis of chloroacetyl polyglycolic acids.²⁷⁶ The method of analysis of the resultant mixture of 1- (55%), 4- (30%), and 3-dibenzofuranacetic acid (15%) was crude, but the results were in accord with simple HMO calculations. The amount of the 1-substituted product is perhaps surprising in view of the steric hindrance at this position.

D. RING-CLEAVAGE REACTIONS

As expected, dibenzofuran is generally stable to reagents such as boiling hydriodic acid, and indeed such reagents are used in the synthesis of dibenzofurans from 2,2'-biphenyldiols. Cleavage of the heterocycle can be achieved, however, by fusion with sodium hydroxide.¹ The presence of activating nitrogroups greatly facilitates this reaction.⁹⁸

When treated with lithium in boiling ether, the heterocycle is cleaved, and subsequent carbonation results in the benzocoumarin **251** (Scheme 67).²⁷⁷ However, if the solvent is dioxane, the intermediate **250** is able to abstract a proton from the solvent and hydrolysis then results in 2-biphenylol.²⁷⁸

²⁷² J. S. Moffatt, *J. Chem. Soc.*, 625 (1951).

²⁷³ E. B. McCall and T. J. Rawlings, British Patent 932,813 [*CA* **60**, 504 (1964)].

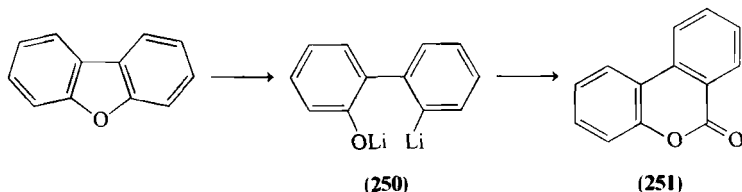
²⁷⁴ H. Gilman and J. Swiss, *J. Am. Chem. Soc.* **66**, 1885 (1944).

²⁷⁵ H. Gilman and S. Avakian, *J. Am. Chem. Soc.* **67**, 349 (1945).

²⁷⁶ P. L. Southwick, M. W. Munsell, and E. A. Bartkus, *J. Am. Chem. Soc.* **83**, 1358 (1961).

²⁷⁷ H. Gilman and D. Esmay, *J. Am. Chem. Soc.* **75**, 2947 (1953).

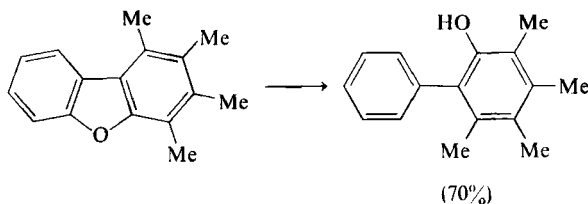
²⁷⁸ H. Gilman and J. Dietrich, *J. Org. Chem.* **22**, 851 (1957).



SCHEME 67

This reaction can also be achieved with sodium and hydrogen at elevated temperature and pressure²⁷⁹ or with sodium hydride at high temperature.²⁸⁰

Cleavage of dibenzofurans, substituted with methyl groups in only one of the benzenoid rings, with 3 atom equiv of lithium in boiling dioxane occurs regiospecifically, and high yields of 2-biphenylols substituted in the phenolic ring are obtained (Scheme 68).²⁸¹ With dibenzofurans, substituted with phenyl groups in only one of the benzenoid rings, the alternative mode of cleavage occurs, and 2-(phenyl-substituted phenyl)phenols results.²⁸²



SCHEME 68

E. METALLATION AND METALLO DERIVATIVES

Bromo-^{283,284} and iododibenzofurans^{285,286} readily form Grignard reagents that undergo the usual reactions. They have been oxidized at low temperature by oxygen to give phenols, usually in low yield.²⁸³ 2-Methoxydibenzofuran-1-ylmagnesium bromide, however, affords 2-methoxy-1-dibenzofuranol in 71% yield under these conditions.⁶³

²⁷⁹ K. W. Müller, U.S. Patent 2,862,035 [CA 53, 9158 (1959)].

²⁸⁰ K. K. Sanko Kagaku, Jpn. Kokai Tokkyo Koho 20,533 [CA 95, 42640 (1981)].

²⁸¹ T. Keumi, C. Murata, Y. Sasaki, and H. Kitajima, *Synthesis*, 634 (1980).

²⁸² T. Keumi, C. Murata, Y. Sasaki, K. Ogasawara, and H. Kitajima, *Nippon Kagaku Kaishi*, 259 (1981) [CA 95, 42537 (1981)].

²⁸³ H. Gilman, W. G. Bywater, and P. T. Parker, *J. Am. Chem. Soc.*, 57, 885 (1935).

²⁸⁴ Monsanto Chemicals Ltd., French Addn. 80, 790 [CA 60, 1704 (1960)].

²⁸⁵ H. Gilman and R. V. Young, *J. Am. Chem. Soc.* 56, 1415 (1934).

²⁸⁶ V. P. Glushkova and K. A. Kochesov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1391 (1957) [CA 52, 7276 (1958)].

Lithiation and mercuration are directed by the oxygen atom and occur at the 4-position, but thallation, achieved by treatment of dibenzofuran with thallium(III) isobutyrate at 110°C, affords the 2-thallium di(isobutyrate), which may be converted to the 2-iodo compound by reaction with iodine.²⁸⁶ Mercuration is achieved by treatment of dibenzofuran with mercury(II) acetate at 150°C, and the resultant 4-mercuric acetate (56%) may also be converted to the iodo compound.²⁸⁵

The 4-sodio and 4-potassio derivatives are known²⁸⁷ but are less convenient to obtain than the 4-lithio derivative, which is readily available by metallation of dibenzofuran with butyllithium.²⁸⁸ Metallation can also be achieved with cross-linked poly(*p*-lithiosytrene) but offers no advantage in yield.²⁸⁹ The 4,6-dimetallo derivatives of dibenzofuran can be made by treatment of dibenzofuran with butyllithium²⁹⁰ or butylsodium.²⁸⁷ Lithiodibenzofurans and dilithiodibenzofurans are also available by bromine-lithium exchange with butyllithium.²⁹¹⁻²⁹³

The lithio derivatives of dibenzofuran undergo the expected reactions. Carbonation yields carboxylic acids,^{288,291-293} reaction with sulfur dioxide yields sulfinic acids,²⁹⁴ and reaction with methyl sulfate yields methyl compounds.^{258,290} Alkylation can also be achieved by treatment of 4-lithiodibenzofuran with alkyl halides.^{295,296} Silylation can be achieved with chlorotrimethyl- or chlorotriphenylsilane.^{214,297} Reaction of lithiodibenzofurans with acetaldehyde^{296,298} and with benzonitrile²²⁹ take the expected course.

The reaction of 4-lithiodibenzofuran with *O*-methylhydroxylamine provides a synthesis of the 4-amino compound,²⁵⁵ and reaction with iodine leads to the iodo compound.²⁷⁵ The reactions of 4-lithiodibenzofuran with tributyl borate,²⁹⁹ diphenyl disulfide,⁵⁵ *N,N*-dimethylcarbamoyl chloride,³⁰⁰ and cyanuric chloride³⁰¹ have been studied.

²⁸⁷ H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **57**, 1121 (1935).

²⁸⁸ H. Gilman and S. Gray, *J. Org. Chem.* **23**, 1476 (1958).

²⁸⁹ D. Braun and F. Seelig, *Chem. Ber* **97**, 3098 (1964).

²⁹⁰ R. Gerdil and E. A. C. Lucken, *J. Am. Chem. Soc.* **87**, 213 (1965).

²⁹¹ H. Gilman, H. B. Willis, and J. Swislowsky, *J. Am. Chem. Soc.* **61**, 1371 (1939).

²⁹² H. Gilman, W. Langham, and H. B. Willis, *J. Am. Chem. Soc.* **62**, 346 (1940).

²⁹³ H. Gilman, J. Swislowsky, and G. E. Brown, *J. Am. Chem. Soc.* **62**, 348 (1940).

²⁹⁴ M. Janczewski and H. Maziarczyk, *Rocz. Chem.* **47**, 449 (1973) [*CA* **79**, 31762 (1973)].

²⁹⁵ W. A. Hewett, J. D. Michaelsen, and J. F. Schimscheimer, U.S. Patent 3,294,763 [*CA* **66**, 38327 (1967)].

²⁹⁶ International Business Machine Corp., British Patent 1,077,086 [*CA* **68**, 78123 (1968)].

²⁹⁷ R. H. Meen and H. Gilman, *J. Org. Chem.* **20**, 73 (1955).

²⁹⁸ W. A. Hewett and E. Gipstein, *J. Polym. Sci., Part B* **6**, 565 (1968).

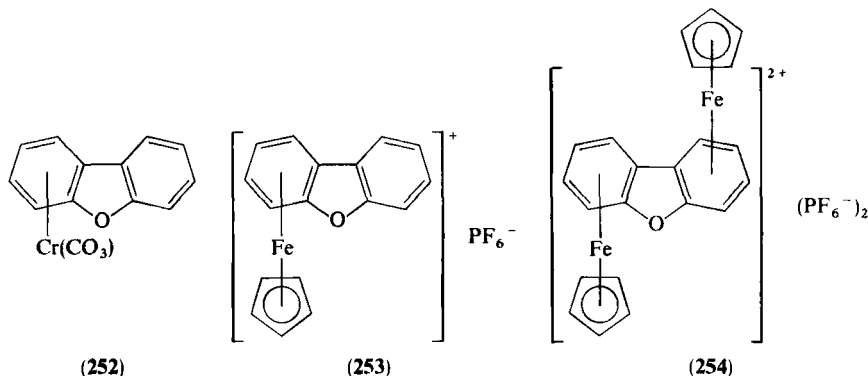
²⁹⁹ J. Yates and R. S. Airs, British Patent 814,647 [*CA* **54**, 8852 (1960)].

³⁰⁰ A. Cattaneo, G. Gelmi, and H. Zevio, *Farmaco Ed. Sci.* **16**, 741 (1961) [*CA* **57**, 5879 (1962)].

³⁰¹ J. B. Chakrabarti, R. W. Goulding, and A. Todd, *JCS Perkin I*, 2499 (1973).

The metallation of substituted dibenzofurans has been little studied. Lithiation of 4-methoxydibenzofuran occurs at the 3- and 6-positions.³⁰² Similarly, 2-methoxydibenzofuran is lithiated at the 1- and 3-positions.³⁰³ 1,3-Dimethoxydibenzofuran, however, is lithiated at the 4-position.³⁰⁴

The chromium tricarbonyl derivative **252**³⁰⁵ and the cyclopentadiene complexes **253** and **254**³⁰⁶ have been prepared.



F. REDUCTION

Hydrogenation of dibenzofuran over a platinum catalyst in acetic acid at 50°C and moderate pressure affords perhydrodibenzofuran.³⁰⁷ At higher temperatures and pressures with platinum or palladium catalysts the product is 2-biphenylol.³⁰⁸ When dibenzofuran is hydrogenated in ethanol over Raney nickel at 190°C and 200 atm for 23 h, the products isolated were: perhydrodibenzofuran (36%), *trans*-2-cyclohexylcyclohexanol (27%), *cis*-2-cyclohexylcyclohexanol (20%), and dicyclohexyl (3%). When the hydrogenation, under these conditions, was terminated after the absorption of only 3 mol equiv of hydrogen, the only product detected was perhydrodibenzofuran.³⁰⁹ Hydrogenation of dibenzofuran over a sodium-rubidium catalyst,

³⁰² H. Gilman, H. B. Willis, T. H. Cook, F. J. Webb, and R. N. Meals, *J. Am. Chem. Soc.* **62**, 667 (1940).

³⁰³ H. Gilman and R. L. Bebb, *J. Am. Chem. Soc.* **61**, 109 (1939).

³⁰⁴ M. V. Sargent and P. Zissiadis, unpublished result.

³⁰⁵ E. O. Fischer, H. A. Goodwin, C. G. Kreiter, H. D. Simmons, K. Sonogashira, and S. B. Wild, *J. Organomet. Chem.* **14**, 359 (1968).

³⁰⁶ C. C. Lee, B. R. Steele, and R. G. Sutherland, *J. Organomet. Chem.* **186**, 265 (1980).

³⁰⁷ H. A. Smith and J. F. Fuzek, *J. Am. Chem. Soc.* **71**, 415 (1949).

³⁰⁸ D. E. Gross and N. A. Fishel, U.S. Patent 4,000,203 [CA **86**, 89385 (1977)].

³⁰⁹ J. I. Jones and A. S. Lindsey, *J. Chem. Soc.*, 1836 (1950).

at 250°C and 80 atm, yielded phenylcyclohexane (80%) and biphenyl (10%).³¹⁰ The hydrogenation of dibenzofuran over tungsten sulfide³¹¹ and molybdenum sulfide³¹² has been studied.

The Birch reduction of dibenzofuran is reported to give 1,4-dihydrodibenzofuran.³¹³ The electrochemical reduction of dibenzofuran by solvated electrons is reported to produce a dihydrodibenzofuran and a tetrahydrodibenzofuran, both of unspecified structure.³¹⁴ Treatment of dibenzofuran with W-7 Raney nickel in boiling methanol gave a moderate yield of *trans*-2-phenylcyclohexanol,³¹⁵ whereas treatment of dibenzofuran with Raney nickel alloy and aqueous sodium hydroxide gave a low yield of 2-biphenylol.³¹⁶

Dibenzofuran³¹⁷ and dimethyldibenzofurans²⁹⁰ yield radical anions on treatment with alkali metals. Their ESR spectra have been studied. The rate constant for the production of the radical anion of dibenzofuran at a stationary mercury electrode has been determined.³¹⁸

G. OXIDATION

Dibenzofuran is highly stable to oxidizing agents. 2-Dibenzofuranol is oxidized to 2-(2-hydroxyphenyl)-1,4-benzoquinone by sodium periodate in aqueous acetic acid,³¹⁹ whereas reaction of 1-dibenzofuranol or 4-dibenzofuranols with Frémy's salt produces the dibenzofuran-1,4-quinones.^{320,321}

The oxidation of dibenzofuran with microorganisms has been studied.³²² A mutant strain of a *Beijerinckia* bacterium oxidizes dibenzofuran to a mixture of *cis*-2,3-dihydroxy-2,3-dihydrodibenzofuran and *cis*-1,2-dihydroxy-1,2-dihydrodibenzofuran. The former compound was found to be too

³¹⁰ S. Friedman, M. L. Kaufman, and I. Wender, *J. Org. Chem.* **36**, 694 (1971).

³¹¹ S. Landa and J. Chuckla, *Sb. Vysoke Skoly Chem.-Technol. Praze, Technol. Paliv.* **5**, 35 (1961) [*CA* **65**, 10555 (1966)].

³¹² S. Landa, A. Mrnkova, and N. Bartova, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv.* **16**, 159 (1969) [*CA* **74**, 99747 (1971)].

³¹³ M. Tomita and T. Ujite, *Yakagaku Zasshi* **81**, 31 (1961) [*CA* **55**, 13442 (1961)].

³¹⁴ M. Miyake, Y. Nakayama, M. Nomura, and S. Kikkaya, *Bull. Chem. Soc. Jpn.* **52**, 559 (1979).

³¹⁵ G. S. Chandler and W. H. F. Sasse, *Aust. J. Chem.* **16**, 20 (1963).

³¹⁶ D. Papa, E. Schwenk, and H. F. Ginsberg, *J. Org. Chem.* **16**, 253 (1951).

³¹⁷ A. G. Evans, P. B. Roberts, and B. J. Tabner, *J. Chem. Soc. B*, 269 (1966).

³¹⁸ H. Kojima and A. J. Bard, *J. Am. Chem. Soc.* **97**, 6317 (1975).

³¹⁹ E. Adler and R. Magnusson, *Acta Chem. Scand.* **13**, 505 (1959).

³²⁰ F. R. Hewgill, T. J. Stone, and W. A. Waters, *J. Chem. Soc.*, 408 (1964).

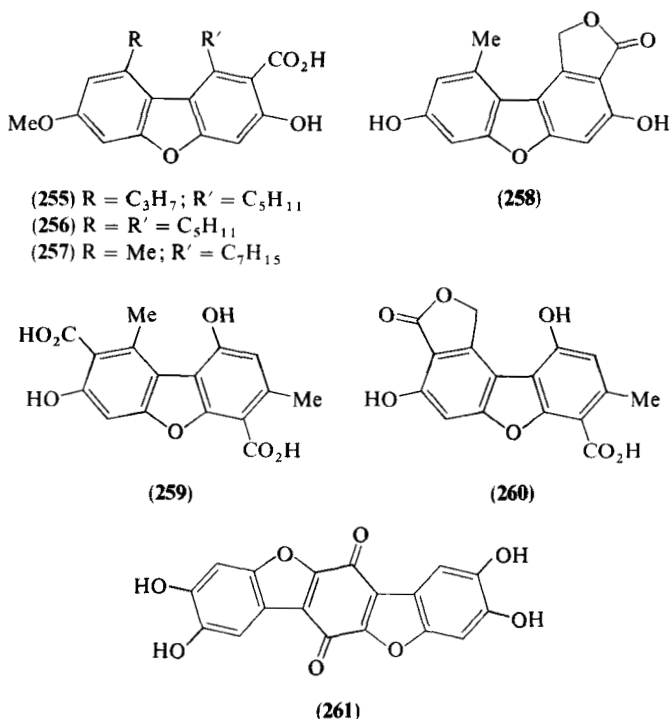
³²¹ F. R. Hewgill and L. R. Mullings, *Aust. J. Chem.* **28**, 355 (1975).

³²² C. E. Cerniglia, J. C. Morgan, and D. T. Gibson, *Biochem. J.* **180**, 175 (1979).

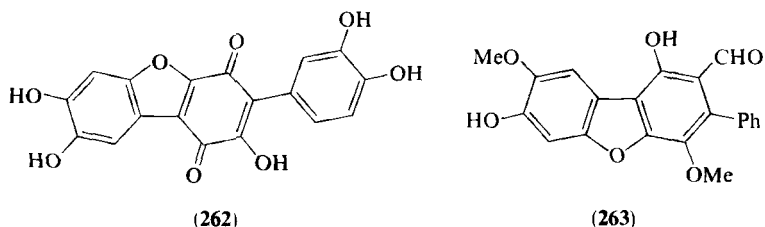
unstable to isolate because it readily decomposed to a mixture of 2- and 3-dibenzofuranols. The stereochemistry of the other metabolite followed from its conversion to an isopropylidene derivative. Fungal oxidation by *Cunninghamella elegans* took a different course and gave *trans*-2,3-dihydroxy-2,3-dihydrodibenzofuran and 2- and 3-dibenzofuranols. The phenols are not artefacts because the diol is only dehydrated to the phenols on heating with acid.

V. Natural Products Related to Dibenzofuran

The majority of natural products related to dibenzofuran are metabolites of lichens or of the higher fungi. The lichen dibenzofurans appear to be formed by carbon-carbon oxidative coupling of orsellinic acid and its homologs. Two modes of coupling are apparent as typified by the group didymic acid (**255**), condidymic acid (**256**), melacarpic acid (**257**),³²³ and strepsilin (**258**); and the other mode of coupling is represented by pannaric



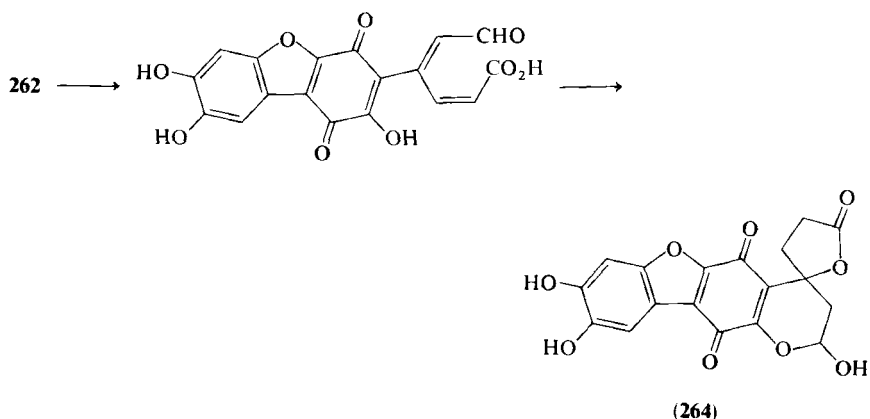
³²³ D. O. Chester and J. A. Elix, *Aust. J. Chem.* **33**, 1153 (1980).



acid (259), schizopeltic acid (112), and porphyrylic acid (260). Dean² has reviewed the chemistry of most of these compounds.

Condidymic acid (256),⁷⁸ pannaric acid (259),²⁷⁰ schizopeltic acid (112),²³ and di-*O*-methylstrepsilin (145)¹²⁸ have been synthesized.

Thelephoric acid (261) occurs in some higher fungi and lichens and its chemistry and synthesis have been reviewed by Thomson.³²⁴ A likely precursor (262) to thelephoric acid (261) has been isolated from *Suillus grevillei* (Klotsch) Sing.³²⁵ Penioflavin, a metabolite of the fungus *Penioflavin sanguinea* Bres. was shown to possess structures 263 by the X-ray method.³²⁶ Hydnuferugin (264) (Scheme 69), isolated from the fungi *Hydnullum ferrugineum* (Fr.) Karsten and *H. zonatum* (Batsch) Karsten, probably arises by oxidative cleavage of the catechol ring in 262.³²⁷ The dibenzofuranoid



SCHEME 69

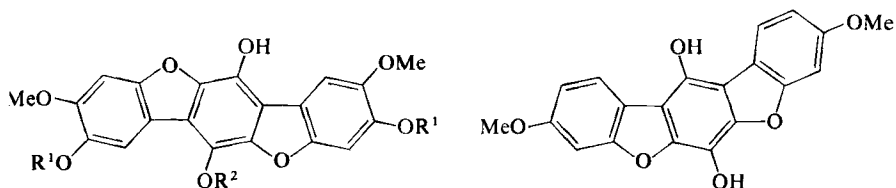
³²⁴ R. H. Thomson, "Naturally Occurring Quinones," 2nd ed. Academic Press, New York, 1971.

³²⁵ R. L. Edwards and M. Gill, *JCS Perkin I*, 351 (1975).

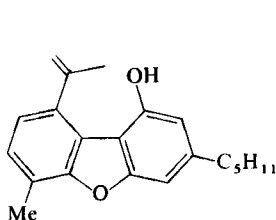
³²⁶ J. Gripenberg, *Acta Chem. Scand., Ser. B*, B32, 75 (1978).

³²⁷ J. Gripenberg, *Tetrahedron Lett.*, 619 (1974).

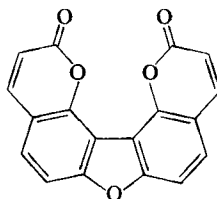
metabolites corticin A (**265**) and B (**266**), close relatives of thelephoric acid, have been isolated from the fungus *Corticium caerulum* (Schrader ex Persoon) Fries as their diacetates.³²⁸ A third pigment, corticin C, is tentatively assigned structure **267**.

(265) $R^1 = H$; $R^2 = Me$ (266) $R^1 = Me$; $R^2 = H$

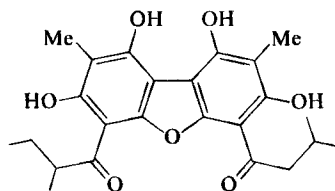
(267)



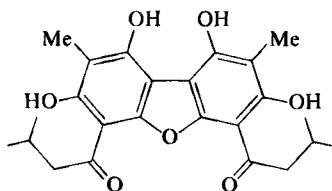
(268)



(269)



(270)



(271)

There are few examples of dibenzofurans occurring in the higher plants. Cannabifuran (**110**) and dehydrocannabifuran (**268**) have been isolated from cannabis in trace amounts.³²⁹ Cannabifuran has been synthesized.²⁴ Rusco-dibenzofuran (**8**) occurs in the roots of *Ruscus aculeatus* L. and its structure was determined by the X-ray method.¹³ Three syntheses have been recorded.^{118,133,134} Gnidicoumarin (**269**) occurs in the roots of *Gnidia*

³²⁸ L. H. Briggs, R. C. Cambie, I. C. Dean, R. Hodges, W. B. Ingram, and P. S. Rutledge, *Aust. J. Chem.* **29**, 179 (1976).

³²⁹ J. Friedrich-Fiechtel and G. Spiteller, *Tetrahedron* **31**, 479 (1975).

lamprantha Gilg., and again its structure was determined by the X-ray method.³³⁰

Two closely related dibenzofurans have been isolated from separate collections of the fruit of the Australian finger cherry, *Rhodomyrtus macrocarpa* Benth.^{85,331} Whether these are genuine metabolites or the result of fungal infection is a matter for speculation.³³² Structures **270** and **271** appear to be the most tenable.¹²

³³⁰ S. M. Kupchan, J. G. Sweeny, T. Murac, M.-S. Shen, and R. F. Bryan, *JCS Chem. Commun.*, 94 (1975).

³³¹ S. Trippett, *J. Chem. Soc.*, 414 (1957).

³³² S. L. Everist, "Poisonous Plants of Australia," p. 386. Angus & Robertson, Sydney, Australia, 1974.

Recent Advances in the Chemistry of 9H-Carbazoles

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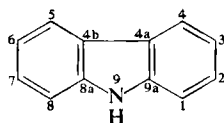
I. Introduction

The chemistry of carbazoles was last reviewed in 1952¹ and 1954² following earlier accounts.^{3,4} More recently, Rodd's first edition coverage⁵ was updated⁶ and halogen derivatives of carbazoles were reviewed.⁷ Alkaloids

¹ W. Freudenberg, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 3, p. 291. Wiley, New York, 1952.

containing a carbazole nucleus have been discussed elsewhere^{8,9} and will not be dealt with in this review, except as aspects of their degradation or synthesis illustrate the fundamental chemistry of carbazoles. Also not covered here is the considerable quantity of work on the polymerization of vinyl- (especially *N*-vinyl-) carbazoles nor the related work on carbazoles as donors in the formation of molecular complexes; both of these have been reviewed elsewhere.^{10,11} Carbazoles have not previously been discussed in this Series though their monoaza analogs, carbolines, have been reviewed.¹² The literature is covered from 1954 to 1982 (*CA* 96) including some earlier references where relevant and some later references as available.

This article deals with the chemistry of carbazoles, and except for their formation from carbazoles as illustrations of the chemistry of carbazoles, it specifically excludes that of 1,2,3,4-tetrahydro-, 1,2,3,4,4a,9a-hexahydro-, 1,2,3,4,5,6,7,8-octahydro carbazoles, etc., because from the viewpoint of chemical reactivity, these are indoles, anilines, pyrroles, and so on. This article also excludes carbazoles with additional fused aromatic or hetero-aromatic rings, again except for the formation of such systems as illustrations of carbazole reactivity. The physical and spectroscopic properties are not covered.



(1) 9H-carbazole

The *CA* full name and numbering system is shown in 1. Tautomers other than 9H-carbazoles are unknown except as reduced derivatives; accordingly,

² W. C. Sumpter and F. M. Miller, *Chem. Heterocycl. Comp.*, **8**, 70 (1954).

³ G. Cohn, "Die Carbazolegruppe." Thieme, Leipzig, 1919.

⁴ N. Campbell and B. M. Barclay, *Chem. Rev.* **40**, 360 (1947).

⁵ T. S. Stevens, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IVA, p. 120. Elsevier, Amsterdam, 1957.

⁶ R. Livingstone, in "Chemistry of Carbon Compounds" (E. H. Rodd ed), Vol IVA, p. 486. 1973.

⁷ J. Kyziol and J. Pielichowski, *Zesz. Nauk. Politech. Krakow.*, *Chem.* **3** (1978) [*CA* **93**, 46253 (1980)].

⁸ R. S. Kapil, in "The Alkaloids" (R. H. F. Manske, ed.), Vol. 13, p. 273. Academic Press, New York, 1971.

⁹ D. P. Chakraborty, *Planta Med.* **39**, 97 (1980) [*CA* **93**, 146231 (1980)].

¹⁰ R. C. Penwell, B. N. Ganguly, and T. W. Smith, *Macromol. Rev.* **13**, 63 (1978).

¹¹ P. Hyde and A. Ledwith, in "Molecular Complexes" (R. Foster, ed.), Vol. 2, Chapter 4. Elek Science, London, 1974; A. Ledwith, *Accs. Chem. Res.* **5**, 133 (1972).

¹² R. A. Abramovitch and I. D. Spencer, *Adv. Heterocycl. Chem.* **3**, 79 (1964).

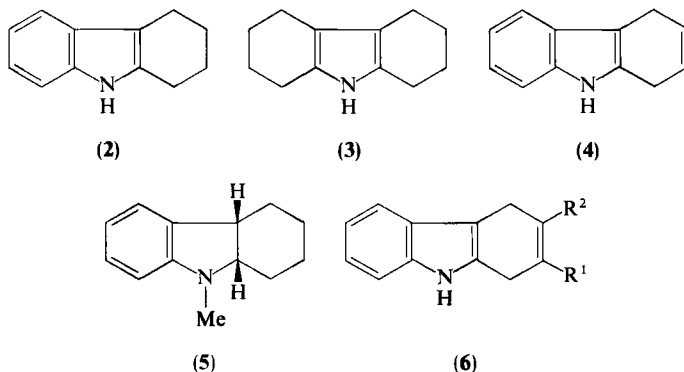
the term *carbazole* used in this review is to be taken as equivalent to 9*H*-carbazole. The presence of a substituent on carbazole nitrogen has been indicated in the literature using either the prefix 9- or the prefix *N*-; both of these will also be used.

II. Chemical Reactions of Carbazoles

A. REACTIONS OF THE NUCLEUS

1. Reduction

Partial catalytic reduction of carbazole tends to stop at 1,2,3,4-tetrahydro- (**2**) or 1,2,3,4,5,6,7,8-octahydro- (**3**) stages. For example, with 5% ruthenium on carbon in decalin at 250 psi and 250°C, **2** is formed in 53% yield,¹³ whereas more vigorous treatment of carbazole or 9-methyl carbazole with hydrogen and the ruthenium catalyst at 500 psi and 200°C caused efficient, complete reduction.¹³ Nickel was reported to catalyze formation of **2** at 320 psi and 250°C¹³ but to give **3** at 100 atm and 260°C.¹⁴ A patent claims¹⁵ the formation of 1,4-dihydrocarbazole (**4**) using Raney nickel, promoted with iron, at 100 to 200 atm in piperidine as solvent. Interestingly, 3-aminocarbazole in acid solution gave 3-amino-1,2,3,4-tetrahydrocarbazole, in poor yield with some recovered starting material, using the 5% ruthenium on carbon catalyst at 100°C and 820 psi.¹³



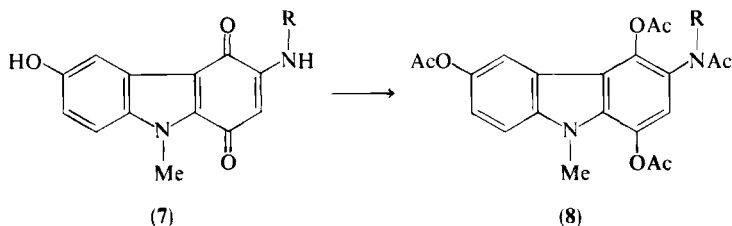
The earliest study of Birch reduction of carbazole showed that both carbazole and 9-methylcarbazole gave the 1,4-dihydro derivatives with

¹³ H. Dressler and M. E. Baum, *J. Org. Chem.* **26**, 102 (1961).

¹⁴ M. Yamada, *Korū Taru* **12**, 668 (1960) [*CA* **61**, 11969c (1964)].

¹⁵ T. Faiziev and A. Safaev, U.S.S.R. Patent 399, 506 [*CA* **80**, P82656g (1974)].

sodium-liquid ammonia-ammonium chloride, whereas using ethanol as a proton source, 1,4-dihydrocarbazole (**4**) and 1,4,5,8-tetrahydro-9-methylcarbazole, respectively, were produced.¹⁶ 9-Methoxymethylcarbazole gave the 1,4-dihydro compound with sodium-liquid ammonia-ammonium chloride but gave mainly the 1,4,5,8-tetrahydro derivative with sodium-liquid ammonia-ethanol. The use of lithium-liquid ammonia-2-propanol seems to be optimal for the production of 1,4-dihydrocarbazole.^{17,18} The combination lithium-n-propylamine gave a high yield of 1,2,3,4-tetrahydrocarbazole but gave equally with 9-methylcarbazole a high yield of 4a,9a-cis-1,2,3,4,4a,9a-hexahydro-9-methylcarbazole (**5**).¹³ Lithium-(or sodium) liquid ammonia treatment of 9-prenylcarbazole gave the 1,4-dihydro derivative efficiently.¹⁹ Birch reduction of 2- and 3-methoxycarbazoles with lithium-liquid ammonia-ethanol led to regioselective reduction of the substituted benzene ring and the formation of 1,4-dihydro derivatives **6** ($R^1 = \text{OMe}$; $R^2 = \text{H}$ and $R^1 = \text{H}$; $R^2 = \text{OMe}$, respectively).²⁰



The quinones **7** ($R = \text{alkyl}$) were reductively acetylated with zinc-acetic anhydride giving **8**.²¹

2. Oxidation

Treatment of carbazole with potassium permanganate in acetone (or nickel peroxide in ether²²) gave mainly 9,9'-bicarbazole **9** (23%) together with the trimer **10** (8%).²³⁻²⁵ In the potassium permanganate oxidation,

¹⁶ S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).

¹⁷ J. W. Ashmore, P. C. Radlick, and G. K. Helmkamp, *Synth Commun.*, 399 (1976).

¹⁸ J. W. Ashmore and G. K. Helmkamp, *Org. Prep. Proced. Int.* **8**, 233 (1976).

¹⁹ M. Julia, F. Le Goffic, and L. D. Matos, *C. R. Hebd. Seances Acad. Sci., Ser. C* **270**, 954 (1970).

²⁰ H. J. Teuber and D. Cornelius, *Justus Liebigs Ann. Chem.* **671**, 127 (1964).

²¹ R. Ott, E. Pinter, and P. Kajtna, *Monatsh. Chem.* **110**, 51 (1979).

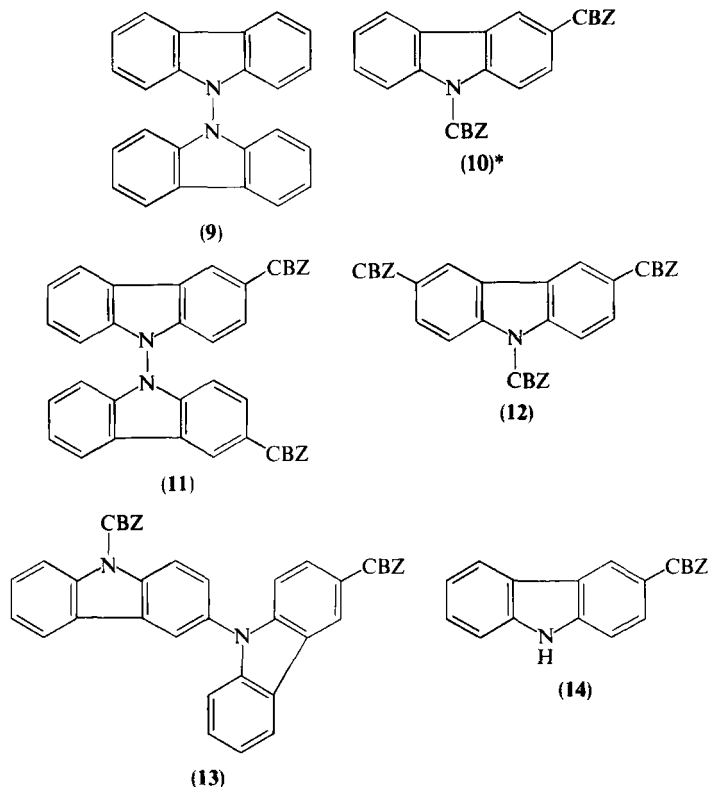
²² J. Sugita, *Nippon Kagaku Zasshi* **88**, 659 (1967) [*CA* **69**, 10319z (1968)].

²³ B. Robinson, *Nature (London)* **210**, 520 (1966).

²⁴ M. Kuroki, *Yuki Gosei Kagaku Kyokaihi* **23**, 447 (1965) [*CA* **63**, 4238d (1965)].

²⁵ W. A. Waters and J. E. White, *J. Chem. Soc. C*, 740 (1968).

the tetramers **11** (7%), **12** (4%), **13** (1%), and the dimer **14** (4%) were also identified.²⁵

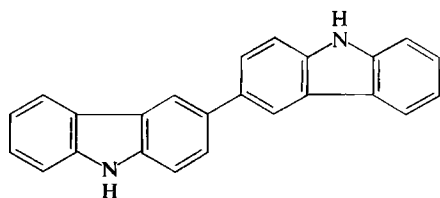


Using potassium permanganate or potassium dichromate in acetic acid solution, only 3,3'-biscarbazole (**15**) is formed²⁴; **9** was not transformed into **15** by acetic acid treatment.²⁴ Palladium acetate in acetic acid also gave **15** and the corresponding 3,3'-dimers with 9-methyl- and 9-ethylcarbazoles.²⁶ Because these coupling processes probably proceed by way of the cation radicals (**16**), it is not surprising that N—N coupling, which requires loss of a proton from nitrogen at some stage, is suppressed in the acidic solvent or by blocking the nitrogen.²⁶ Conversely, blocking both 3- and 6-positions leads to N—N coupled dimers, as with the 3,6-dihalocarbazoles.²⁷

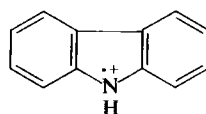
²⁶ I. V. Kozhevnikov, S. A. Tuzovskaya, V. P. Lopatinskii, V. M. Sutyagin, O. V. Rotar, and K. I. Matveev, *React. Kinet. Catal. Lett.* **9**, 287 (1978).

²⁷ Z. J. Allen and F. Mužik, *Chem. Listy* **50**, 1808 (1956); *Collect. Czech. Chem. Commun.* **22**, 64 (1957).

*In this and succeeding structures, CBZ is used to denote the 9-carbazolyl substituent.

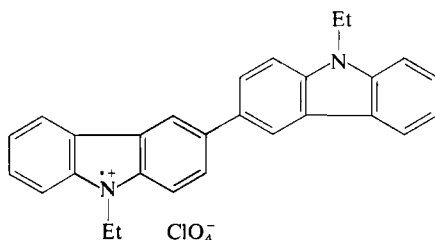


(15)



(16)

Under suitable conditions, further oxidation of the coupled products produces isolable dimer cation radicals. Thus treatment of 9-alkylcarbazoles with lead tetracetate in acetic acid–perchloric acid,²⁸ or with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in acetic acid–perchloric acid,²⁹ or with tris-(*p*-bromophenyl)ammoniumyl perchlorate in methylene chloride,²⁹ or with nitrosonium borofluoride in acetonitrile³⁰ all gave isolable cation radical perchlorates such as 17. These were reducible with aqueous sodium dithionite to the corresponding bicarbazoles; the dimer cation radicals could be produced again by reoxidation of the dimer using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in acid solution.²⁹



(17)

The formation of bicarbazoles can also be achieved electrolytically in acetonitrile solution; once again, at the anode, the carbazole cation radical is produced and dimerizes.^{31–35} The further oxidation of 3,3'-bicarbazole under these conditions with loss of two electrons and formation of a dication–diradical was demonstrated.³¹ Anodic oxidative coupling³² occurs at nitrogen best in the presence of collidine, presumably via deprotonation,

²⁸ D. H. Iles and A. Ledwith, *Chem. Commun.*, 498 (1968).

²⁹ P. Beresford, D. H. Iles, L. J. Kricka, and A. Ledwith, *J. C. S. Perkin I*, 276 (1974).

³⁰ B. K. Bandlish and H. J. Shine, *J. Org. Chem.* **42**, 561 (1977).

³¹ J. F. Ambrose and R. F. Nelson, *J. Electrochem. Soc.* **115**, 1159 (1968).

³² J. F. Ambrose, L. L. Carpenter, and R. F. Nelson, *J. Electrochem. Soc.* **122**, 876 (1975).

³³ W. Lamm, F. Pragst, and W. Jugelt, *J. Prakt. Chem.* **317**, 995 (1975).

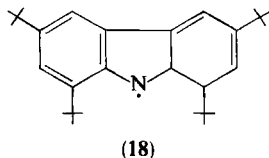
³⁴ P. Kubacek, *Collect. Czech. Chem. Commun.* **46**, 40 (1981).

³⁵ J. M. Bobbitt, C. L. Kulkarni, and J. P. Willis, *Heterocycles* **15**, 495 (1981).

and blocking 9- and 3-positions leads^{32,33} to 6,6'-coupling. 9,9'-Bicarbazole, 9,9'-diethyl-3,3'-difluoro-6,6'-bicarbazole, 3,3',6,6'-tetrabromo-9,9'-bicarbazole, 9,9'-di-(*p*-methoxyphenyl)-3,3'-bicarbazole, 9,9'-di(*p*-nitrophenyl)-3,3'-bicarbazole,³² and 9,9'-diphenyl-3,3'-bicarbazole³³ were all prepared in high yield on a preparative scale by this method. These results emerged from an extensive study of anodic oxidation of nearly 80 carbazoles.³² Electrooxidation of carbazoles has been briefly reviewed.³⁵

A species believed to be the monomer cation radical of 9-ethylcarbazole as a green solution in acetonitrile formed by oxidation of 9-ethylcarbazole with iodine-silver(I) perchlorate, was detected by ESR spectroscopy, although the perchlorate of the cation radical could not be isolated; subsequent treatment with potassium iodide gave 9,9'-diethyl-3,3'-bicarbazole.³⁶ The borofluoride salts generated as crystalline materials by oxidation of carbazole or 9-methylcarbazole with tropylium borofluoride in acetonitrile followed by precipitation with methanol³⁷ are not salts of the monomer cation-radical³⁸ as originally believed.³⁷ Russian workers have suggested that nitration of carbazole proceeds via a cation radical.³⁹

Neutral carbazolyl radicals can be produced and even crystallized providing the nitrogen and the 3- and 6-positions are sufficiently hindered and blocked, respectively. For example blue-black crystals of 1,3,6,8-tetra-*tert*-butylcarbazolyl (**18**) were obtained by oxidation of the 9-lithio salt (see Section II,A,3) of 1,3,6,8-tetra-*tert*-butylcarbazole with iodine.^{40,41} Lead dioxide is the more usual oxidant, usually in benzene solution using the lithium salt of the carbazole.^{40,42} Fewer bulky groups allow dimerization processes to occur but with interesting regio differences to those previously described, which proceed via cation radicals. For example, whereas potassium permanganate in acetone converts 3,6-di-*tert*-butylcarbazole to 3,3',6,6'-tetra-*tert*-butyl-9,9'-bicarbazole, iodine oxidation of the lithium salt gives mainly the 1,9'-coupled dimer **19** (R = H).⁴² In the comparable formation



³⁶ B. K. Bandlish and H. J. Shine, *J. Heterocycl. Chem.* **12**, 287 (1975).

³⁷ A. Ledwith and M. Sambhi, *Chem. Commun.*, 64 (1965).

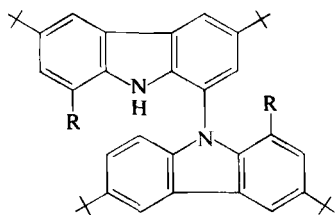
³⁸ Professor A. Ledwith, personal communication (1982).

³⁹ A. S. Morkovnikov, N. M. Panov, and O. Yu. Okhlobystin, *Dokl. Akad. Nauk SSSR* **251**, 125 (1980) [*CA* **93**, 131740j (1980)]; cf. C. L. Perrin, *J. Am. Chem. Soc.* **99**, 5516 (1977).

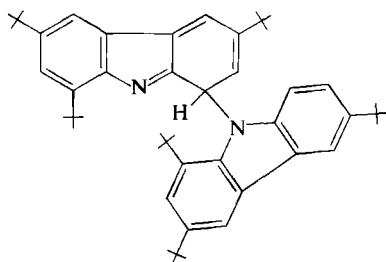
⁴⁰ F. A. Neugebauer and H. Fischer, *Angew. Chem., Int. Ed. Engl.* **10**, 732 (1971).

⁴¹ H. Eger, A. Rieker, and E. Müller, *Tetrahedron* **32**, 2579 (1976).

⁴² F. A. Neugebauer, H. Fischer, S. Bamberger, and H. O. Smith, *Chem. Ber.* **105**, 2694 (1972).



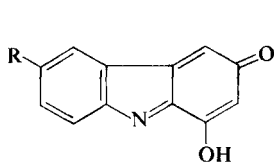
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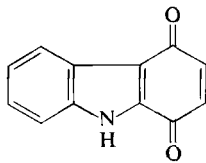
(20)

of **19** ($R = t\text{-Bu}$), the intermediate **20** could be detected by NMR spectroscopy.⁴² 1,8-Di-*tert*-butylcarbazole on successive treatments with butyllithium and then iodine gave the 3,3'-linked dimer.⁴²

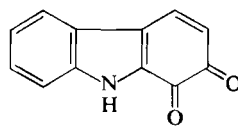
Carbazole, 9-methyl- and 9-acetylcarbazoles give **21** ($R = \text{H}$) and 3-acetyl-, 3-acetyl-9-methyl-, 3,6-diacetyl-, and 3,6-diacetyl-9-methylcarbazoles give **21** ($R = \text{Ac}$) on exposure to light from a xenon lamp in ethanolic sulfuric acid at 4°C in the presence of air. The transformations were explained by postulating initial photolytic cleavage to carbazole or 3-acetylcarbazole, respectively, followed by attack by singlet oxygen.⁴³



(21)



(22)



(23)

1-Hydroxycarbazole gave the *p*-quinone (**22**) and 2-hydroxycarbazole the *o*-quinone (**23**) on oxidation with potassium nitrosodisulfonate.⁴⁴

3. Acidity and Basicity

Carbazole is a weak acid and will form salts with strong bases by loss of the *N*-hydrogen. These salts provide the usual means for the introduction of substituents onto the nitrogen atom (see Section II,B). The pK_a of carbazole is 17.1 (extrapolated value in water)⁴⁵ or 19.9 in dimethyl sulfoxide.⁴⁶ This

⁴³ G. N. Ivanov, V. Ya. Tolmacheva, V. P. Lopatinskii, O. V. Rotar, T. G. Vedernikova, G. S. Yakusheva, and G. M. Samoilenko, *Izv. Tomsk. Politekh. Inst.* **257**, 101 (1973).

⁴⁴ H. J. Teuber and G. Staiger, *Chem. Ber.* **87**, 1251 (1954); **92**, 2395 (1959).

⁴⁵ R. Gaboriaud, J.-C. Halle, and P. Letellier, *Bull. Soc. Chim. Fr.*, 1093 (1976).

⁴⁶ F. G. Bordwell, G. E. Drucker, and H. E. Fried, *J. Org. Chem.* **46**, 632 (1981); M. I. Terekhova, E. S. Petrov, E. M. Rokhlina, D. N. Kravtsov, and A. I. Shatenshtein, *Khim. Geterotsikl. Soedin.*, 1104 (1979) [*CA* **92**, 41088c (1980)].

last value can be compared with values of 20.9 and 23.1 for indole and pyrrole, respectively, in the same solvent.⁴⁶ Electron-withdrawing groups further acidify the *N*-hydrogen, pK_a values of 14.2 and 13.1 being measured for 3-nitrocarbazole^{47,48} and 3,6-dinitrocarbazole,⁴⁷ respectively, in aqueous hydrazine as solvent.⁴⁷ A comparison with the pK_a values of 16.4 and 14.5 for *N*-4-nitrophenylphenylamine and 4,4'-dinitrodiphenylamine, respectively, gives a measure of the extra stabilization of the *N*-anion within the carbazole system.⁴⁷ Soviet workers reported the following order of decreasing pK_a values (i.e., increasing acidities): $\text{Ph}_2\text{NH} > \text{indole} > \text{carbazole} > \text{pyrrole} > 3\text{-chlorocarbazole} > 3,6\text{-dichlorocarbazole} > 3,6\text{-dibromocarbazole} > 3\text{-nitrocarbazole} > 3,6\text{-diacetylcabazole} > 3,6\text{-dinitrocarbazole}$.⁴⁹ The solubility of 3,6-dinitrocarbazole in aqueous sodium hydroxide was used to separate it from its 1,6-dinitro isomer.⁵⁰

With the carbazole nitrogen blocked, the most acidic proton in *N*-alkylcarbazoles is that at C-1⁵¹⁻⁵³; it is significant that the most acidic proton in 9-phenylcarbazole is the ortho proton on the phenyl substituent.⁵¹

Carbazole is a very weak base, proton addition occurring at the nitrogen which is easily diagnosed by the change in characteristic carbazole UV absorption to that typical of fluorene.⁵⁴ The weak basicity can be used to evaluate the resonance energy of carbazole.^{54a} The following ρK_a values for *N*-protonation of some substituted carbazoles were measured in sulfuric acid: carbazole (−6.8), 9-methyl-carbazole (−8.3), 3-methylcarbazole (−5.4), 2-methoxycarbazole (−6.3), 2-bromocarbazole (−7.8), 3,6-dichlorocarbazole (−8.2), and 2-nitrocarbazole (−7.0).⁵⁴

4. Electrophilic Substitution: General Discussion

The most reactive position is C-3, followed by C-1. Treatment of 1,2-, 3,4,5,6,7,8-octadeuteriocarbazole with hydrogen chloride in ethanol at 30°C gave 2,4,5,7-tetradeteriocarbazole.⁵⁵ 9-Acylcarbazoles, in which the aro-

⁴⁷ N. C. Deno, *J. Am. Chem. Soc.* **74**, 2039 (1952).

⁴⁸ R. Stewart and J. P. O'Donnell, *J. Am. Chem. Soc.* **84**, 493 (1962).

⁴⁹ I. P. Zharebtsov and V. P. Lopatinskii, *Izv. Tomsk. Politekh. Inst.* **163**, 12 (1970) [*CA* **75**, 117862x (1971)].

⁵⁰ H. M. Grotta, C. J. Riggle, and A. E. Bearse, *J. Org. Chem.* **29**, 2474 (1964).

⁵¹ H. Gilman and S. M. Spatz, *J. Org. Chem.* **17**, 860 (1952).

⁵² H. Gilman and S. Gray, *J. Org. Chem.* **23**, 1476 (1958).

⁵³ W. E. Noland and G. J. Meisters, *J. Org. Chem.* **25**, 2060 (1960).

⁵⁴ H. J. Chen, L. E. Hakka, R. L. Hinman, A. J. Kresge, and E. B. Whipple, *J. Am. Chem. Soc.* **93**, 5102 (1971).

^{54a} M. C. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron* **32**, 1767 (1976).

⁵⁵ F. A. Neugebauer, *Chem. Ber.* **106**, 1716 (1973).

matic character of the central ring is reduced, tend to react rather more like biphenyls giving a higher percentage of attack at C-2.

These trends have been quantified for some reactions. Nitration studies showed carbazole to react 222,000 times faster than benzene, with nitric acid-acetic anhydride having partial rate factors of 32,100 (C-1), 1,100 (C-2), 77,600 (C-3), and too small to measure (C-4).⁵⁶ Carbazole reacts about 20 times more slowly than diphenylamine. The partial rate factor for nitration at C-3 can be compared with a value of 50,100 found for the perchloric acid protodesilylation of 3-trimethylsilylcarbazole.⁵⁷

An explanation for the relatively low value of the partial rate factor at C-1 compared with the ortho positions in diphenylamine has been given in terms of the greater strain present in the transition state for substitution in the tricyclic system.⁵⁸

Chlorination of 9-acetylcarbazole in acetic acid produced values of 4,300 (C-1), 8,600 (C-2), 122,000 (C-3), and 8,600 (C-4) for the partial rate factors. Chlorination of carbazole itself gave values of $> 10^7$ and $> 10^8$ for the 1- and 3-positions; chlorination of carbazole was found to be six times slower than that of diphenylamine.⁵⁹

Despite the relative figures for chlorination of 9-acetylcarbazole, electrophilic substitution of 9-acylcarbazoles has been used preparatively to produce 2-nitro-⁶⁰ and 2-acylcarbazoles.⁶¹⁻⁶⁶ 9-Nitrosocarbazole nitrates at C-3.

In the acetylation of carbazole using dimethylacetamide-phosgene in methylene chloride, attack was shown to occur mainly at nitrogen (93:7, N:C-3)⁶⁷; trifluoroacetylation proceeded exclusively at nitrogen.⁶⁸ Carbazole was more reactive in this sense than indole and much more reactive than pyrrole, a result paralleling their respective basicities at nitrogen^{67,68} (see Section II,A,3). N-Acylation under these conditions is thought to involve

⁵⁶ M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 3079 (1958).

⁵⁷ C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961).

⁵⁸ R. Taylor, *J. Chem. Soc. B.*, 1559 (1968).

⁵⁹ P. B. D. de la Mare, O. M. H. El Dusouqui, and E. A. Johnson, *J. Chem. Soc. B*, 521 (1966);

P. B. D. de la Mare, M. A. Wilson, O. M. H. El Dusouqui, *J. C. S. Perkin II*, 634 (1974).

⁶⁰ J. B. Kyziol and A. Domanski, *Org. Prep. Proced. Int.* **13**, 419 (1981)

⁶¹ J. B. Kyziol and A. Lyzniak, *Tetrahedron* **36**, 3017 (1980).

⁶² H. Hannig and B. Schobless, *Pharmazie* **18**, 456 (1963).

⁶³ E. Chiellini, R. Solaro, and A. Ledwith, *Makromol. Chem.* **178**, 701 (1977).

⁶⁴ J. Schmitt, M. Suquet, and R. Falland, *Bull. Soc. Chim. Fr.*, 1470 (1957).

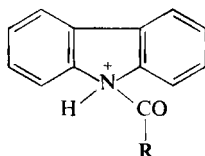
⁶⁵ L. Berger, A. J. Corraz, D. R. Parrish, and J. W. Scott, U.S. Patent 4,150,031 [CA **91**, P157594y (1979)].

⁶⁶ H. Leditschke, *Chem. Ber.* **86**, 612 (1953).

⁶⁷ A. Cipiciani, S. Clementi, P. Linda, G. Marino, and G. Savelli, *J. C. S. Perkin II*, 1284 (1977).

⁶⁸ A. Cipiciani, S. Clementi, P. Linda, G. Savelli, and G. V. Sebastiani, *Tetrahedron* **32**, 2595 (1976).

an intermediate such as **24**, in which only the aromaticity associated with the central ring has had to be lost. In accord with this idea, the study of trifluoroacetylation showed pyrrole and indole to undergo attack at nitrogen to the extent of 0 and 58%, respectively.⁶⁸



(24)

From a consideration of the further substitution of C-substituted carbazoles, a straightforward picture emerges, in so far as results are available (see Section II,D for examples and references). An alkyl or aryl group on carbazole nitrogen does not alter the strong tendency for 3-electrophilic substitution, but reactions are slower.

The presence of a 3-substituent, whether electron withdrawing or donating, leads to substitution at C-6. In carbazoles with 3-substituents, reaction leading to a ring closure involving that substituent are known at either C-2 or C-4. 3,6-Disubstituted carbazoles (whether the groups are deactivating or activating) undergo electrophilic attack at C-1 or C-8. Forcing conditions usually produce 1,3,6,8-tetrasubstituted carbazoles; forcing sulfonation gives the 2,3,6,8-tetrasulfonic acid.

Much less is known of the substitution of 1-, 2-, or 4-substituted carbazoles, undoubtedly because, as emerges from the foregoing discussion, they are much less readily accessible. An activating group at C-2 leads to substitution at C-1 and C-3, the latter predominating. 1,4-Dimethylcarbazoles react with electrophiles at C-3; not surprisingly, this is also true with the additional presence of deactivating groups at C-6. More significant is the continued pattern of 3-substitution of 1,4-dimethylcarbazoles even when two strongly activating groups are present at C-6 and C-7.

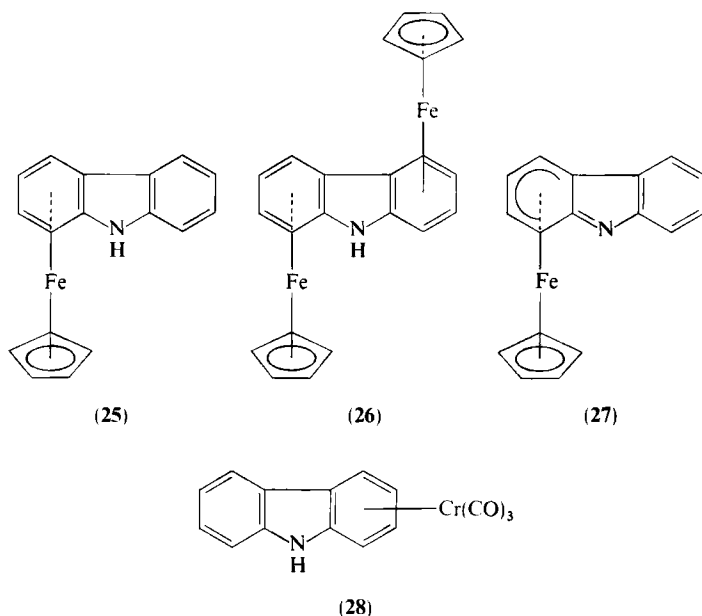
5. Organometallic Derivatives

Carbazole will react with 1 or 2 mol of ferrocene in hot decalin in the presence of aluminium-aluminium chloride producing crystalline derivatives in which either one⁶⁹ or both⁷⁰ of the benzene rings is linked to iron, **25** and **26**, respectively. The sandwich compound **25** was deprotonated to **27** with sodamide in liquid ammonia.⁶⁹ A chromium carbonyl complex **28**

⁶⁹J. F. Helling and W. A. Hendrickson, *J. Organomet. Chem.* **141**, 99 (1977).

⁷⁰C. C. Lee, B. R. Steele, and R. G. Sutherland, *J. Organomet. Chem.* **186**, 265 (1980).

has also been obtained by reaction with chromium hexacarbonyl in refluxing di-*n*-butyl ether.⁷¹



B. INTRODUCTION OF SUBSTITUENTS ONTO CARBAZOLE NITROGEN

In most, but not all, instances substituents are introduced onto the carbazole nitrogen via a carbazol-9-yl anion formed by base N-deprotonation. It seems now that the conditions often used in earlier work to generate the carbazol-9-yl anion were unnecessarily severe and that much milder conditions can be utilized. Anionic carbazole nitrogen, in common with other heteroanionic centers, is about 80 times less nucleophilic than a pK_a -comparable carbanionic center.⁷² The order of reactivity is carbazole > 3-chlorocarbazole > 3,6-dichlorocarbazole > 3-nitrocarbazole in the reaction of the corresponding 9-yl anions with ethylene oxide. This illustrates the relative stabilities of these anions as measured by the acidities of the carbazoles⁷³ (see Section II,A,3); the more acidic the carbazole, the more stable and less reactive its anion as a nucleophile.

⁷¹ E. O. Fischer, H. A. Goodwin, C. G. Kreiter, H. D. Simmons, K. Sonogashira, and S. B. Wild, *J. Organomet. Chem.* **14**, 359 (1968).

⁷² F. G. Bordwell and D. L. Hughes, *J. Org. Chem.* **47**, 169 (1982).

⁷³ V. P. Lopatinskii, I. P. Zherebtsov, and L. I. Tsybul'nik, *Izv. Tomsk. Politekh. Inst.* **163**, 8 (1970).

1. Alkyl

The fusion of powdered potassium hydroxide and carbazole together at 220–260°C has been often used for the preparation of the potassium salt of carbazole, the salt then being utilized in hydrocarbon solvent; powdered potassium hydroxide was shown⁷⁴ to be better for this purpose than strong aqueous sodium hydroxide. Many 9-alkylations have been conducted in this way including preparations of dicarbazol-9-ylalkanes⁷⁵ [**29**: R = (CH₂)_{3–6}-carbazol-9-yl] (using the corresponding dihalides), 9-(2,3-epoxyprop-1-yl)⁷⁶



29: R = CH₂CHCH₂ (using epichlorhydrin), (**29**: R = 3-carboxypropyl)⁷⁷ (using butyrolactone), 9-allylcarbazole⁷⁸ (**29**: R = CH₂CH=CH₂) (using allyl bromide), 9-bromoalkylcarbazoles⁷⁸ (**29**: R = (CH₂)_{4–6}Br) (using the dibromides), and 9-(prop-1-yn-3-yl)carbazole⁷⁹ (**29**: R = CH₂C≡CH) (using 3-bromoprop-1-yne). Other workers have not preformed the carbazole salt but used powdered KOH and, as solvent, acetone, to make a range⁸⁰ of 9-*n*-alkylcarbazoles (**29**: R = (CH₂)_{4–7}CH₃) and 3-isobutyl-9-(2-chloroethyl)carbazole⁸³ (using the tosylate of 2-chloroethanol) or using dimethylsulfoxide as solvent to give the ether⁸¹ [**29**: R = (CH₂)₂OCH=CH₂] (from the chloro compound), or in chlorobenzene with triethanolamine to give 9-ethylcarbazole⁸² (using ethyl phenylsulfonate). Carbazol-9-ylsodium in dimethylformamide gave the sugar derivative⁸³ (**29**: R = **30**) (from a precursor epoxide). A “solid HMPT,” that is a polymer-bound derivative of hexamethylphosphoric triamide, was used to facilitate the conversion of carbazol-9-ylsodium in tetrahydrofuran to 9-methyl-, -ethyl-, -benzyl-, and -allyl derivatives in high yield.⁸⁴ Barium oxide in dimethylformamide was employed for the N-methylation and N-benzylation of 1,3,6,8-tetra-*tert*-butyl-

⁷⁴ V. P. Lopatinskii, E. E. Sirotkina, and M. M. Anosova, *Tr. Tomsk. Gos. Univ., Ser. Khim.* **170**, 49 (1964) [*CA* **63**, 565d (1965)].

⁷⁵ E. Hannig and B. Schobess, *Pharm. Zentralhalle* **102**, 500 (1963).

⁷⁶ A. Stanisauskite and K. Meskauskas, *Deposited Doc.* VINITI 1109 (1976) [*CA* **89**, 146705k (1978)]; I. M. Eznielev and N. A. Larin, *Zh. Obshch. Khim.* **26**, 791 (1956) [*CA* **50**, 14710e (1956)].

⁷⁷ W. Reppe and co-workers, *Justus Liebigs Ann. Chem.* **596**, 158 (1955).

⁷⁸ J. Heller, D. L. Lyman, and W. A. Hewett, *Makromol. Chem.* **73**, 48 (1964).

⁷⁹ K. C. Yee, U.S. Patent 4,125,534 [*CA* **90**, P88046m (1979)].

⁸⁰ V. P. Lopatinskii, E. E. Sirotkina, M. M. Anosova, L. G. Tikhonova, and S. F. Pavlov, *Izv. Tomsk. Politekh. Inst.* **126**, 62 (1964) 58 [*CA* **63**, 18008c (1965)].

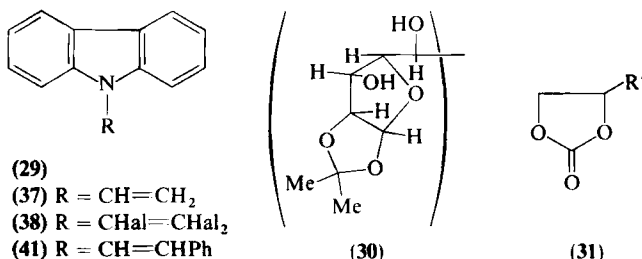
⁸¹ S. R. Turner and D. M. Pai, *Macromolecules* **12**, 1 (1979).

⁸² J. Gnilka, *Biul. Inf. Barwniki Srodki Pomocnicze* **17**, 10 (1974) [*CA* **82**, 45003m (1975)].

⁸³ S. Ya. Mel'nik, E. A. Utkina, M. N. Preobrazhenskay and N. N. Suvorov, *Zh. Org. Khim.* **10**, 750, (1974) [*CA* **81**, 25862t (1974)].

⁸⁴ Y. Leroux and H. Normant, *C. R. Hebd. Seances Acad. Sci., Ser. C.* **285**, 241 (1977).

carbazole.⁸⁵ The combination 85% aqueous potassium hydroxide in diglyme provided the means for the preparation of fluoroalkyl derivatives **29** ($R = CF_2CF_2H$ and $R = CF_2CFHCF_3$), (using tetrafluoroethene and hexafluoropropene, respectively).⁸⁶



Sodium ethoxide in dimethylformamide converted carbazole and epichlor-

hydrin efficiently to **29** ($R = CH_2CH(O)CH_2$),⁸⁷ and the same base employed in benzene, nitrobenzene, and chlorobenzene solutions promoted Michael additions of the 3-nitrocarbazol-9-yl, 3,6-dinitrocarbazol-9-yl, and 3-aminocarbazol-9-yl anions, respectively, to acrylonitrile giving their 9-(2-cyanoethyl) derivatives.⁸⁸

The use of potassium carbonate allowed carbazole to be converted to the hydroxyalkyl derivatives **29** ($R = CH_2CH(OH)R'$) by reaction with the carbonates **31** ($R' = H$ or Me).⁸⁹

Carbazole can be more easily converted fully and irreversibly to its *N*-anion by bases stronger than potassium or sodium hydroxide: amide and hydride bases under anhydrous conditions have been employed. Thus, sodium amide in liquid ammonia was utilized with the appropriate halide for the preparation of 9-(prop-1-yn-3-yl)carbazole (**29**: $R = CH_2C\equiv CH$)^{90,91} and 9-methylcarbazol-1-ylcarboxylic acid⁵³, the preparation of 3-dimethylamino-9-(2-hydroxyethyl)carbazole from ethylene oxide utilized sodium amide in

⁸⁵ F. A. Neugebauer and H. Fischer, *Chem. Ber.* **105**, 2686 (1972).

⁸⁶ V. G. Poludnenko and A. L. Bel'ferman, *Khim. Geterotsikl. Soedin.*, 118 (1980) [*CA* **92**, 180937s (1980)].

⁸⁷ Kh. Akhmedov, M. G. Chauser, and M. I. Cherkashin, *Deposited Doc.* VINITI 2609 (1978) [*CA* **91**, 211190d (1979)].

⁸⁸ M. K. Murshtein, V. I. Shishkina, and Z. V. Pushkareva, *Zh. Prikl. Khim.* **36**, 644 (1963) [*CA* **59**, 10267d (1963)].

⁸⁹ J. Degutis and A. Urbonavicius, *Chem. Chem. Technol., Tech. Mokslu Isvystymo Resp. Ju Rezult. Panaudojimo Konf. Medziaga*, 25 (1974) [*CA* **86**, 55233j (1977)].

⁹⁰ J.-L. Dumont, *C. R. Hebd. Seances Acad. Sci.* **261**, 1710 (1965).

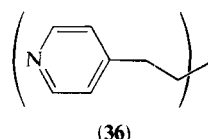
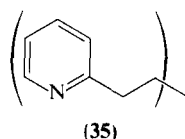
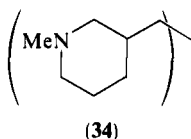
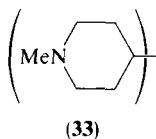
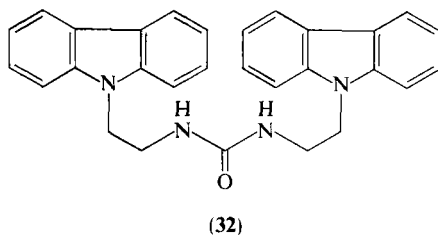
⁹¹ K. C. Yee and R. R. Chance, *J. Polym. Sci., Polym. Phys. Ed.* **16**, 431 (1978).

toluene solution⁹² as did the alkylation of 2-propionylcarbazole to give a range of 9-dimethylaminoalkyl derivatives from the corresponding halides $\text{Hal}(\text{CH}_2)_{2-3}\text{NMe}_2$ and $\text{HalCH}_2\text{CHMeNMe}_2$.⁶⁴ This base in xylene gave 9-(pyridin-2-ylmethyl)carbazole⁹³ and 9-*n*-butyl-carbazole,⁹⁴ again from the halides.

Sodium hydride as base with epichlorhydrin was utilized to prepare **29**

($\text{R} = \text{CH}_2\text{CH}(\text{O})\text{CH}_2$),⁹⁵ dimethyl formamide with the bromide to prepare **29** ($\text{R} = \text{CH}_2\text{C}\equiv\text{CH}$),⁹⁶ and tetrahydrofuran to prepare the 9-(3-dimethylaminopropyl) derivatives of the four isomeric nitrocarbazoles using the tosylates as alkylating agents.⁹⁷

The ethyl urethane of aziridine was attacked by the carbazole anion generated using sodium to give **32**⁹⁸, lithium hydride in xylene provided the means for the preparation of **29** ($\text{R} = \text{33}$ and $\text{R} = \text{34}$) from the corresponding bromides.⁹⁹



A catalytic quantity of potassium in pyridine solution catalyzed the Michael-type addition of carbazole to 2- and 4-vinylpyridine giving **29** ($\text{R} = \text{35}$ and $\text{R} = \text{36}$)¹³; comparable addition to 2-methyl-5-vinylpyridine

⁹² A. Minami, K. Morimoto, and Y. Murakami, *Nippon Kagaku Zasshi* **85**, 880 (1964) [*CA* **62**, 14612e (1965)].

⁹³ Chemische Fabrik Promonta G.m.b.H., British Patent 822,592 [*CA* **54**, 4628d (1960)].

⁹⁴ Ng. Ph. Buu-Hoi and R. Royer, *J. Org. Chem.* **16**, 1198 (1951).

⁹⁵ Y. Inaki, G. Sheybani, and K. Takemoto, *Technol. Rep. Osaka Univ.* **25**, 249 (1975) [*CA* **83**, 59374s (1975)].

⁹⁶ J. L. Dumont, W. Chodkiewicz, and P. Cadiot, *Bull. Soc. Chim. Fr.*, 1197 (1967).

⁹⁷ A. Ledochowski and J. A. Zirra, *Rocz. Chem.* **49**, 1179 (1975) [*CA* **84**, 59095x (1976)].

⁹⁸ H. Stamm and W. Wiesert, *Chem. Ber.* **111**, 502 (1978).

⁹⁹ Chemische Fabrik Promonta G.m.b.H., British Patent 809,488 [*CA* **53** P14129c (1959)].

has been reported,¹⁰⁰ although it seems less in line with the properties of the vinylpyridines.

Rather different are two N-alkylations effected with mercuric acetate: 9-(3-oxobut-1-yl)carbazole (**29**; R = CH₂CH₂COCH₃) was formed from carbazole and but-1-en-3-yne in ethanolic solution containing a trace of concentrated sulfuric acid,¹⁰¹ and a low yield of 9-allylcarbazole was produced on reaction with allyl alcohol in benzene¹⁰².

Heating with triethyl-*N*-2-methylphenylphosphorimidate or related compounds converts carbazole to 9-ethylcarbazole efficiently, whereas triethyl phosphite will not N-alkylate efficiently.¹⁰³

Iron acetylacetonate catalyzed the introduction of a range of alkyl groups onto the carbazole nitrogen using the corresponding halides.¹⁰⁴ A small yield of 9-(2-cyanoethyl)carbazole was obtained by light catalyzed addition of carbazole to acrylonitrile.¹⁰⁵

The preparatively useful and simple N-alkylation procedure that utilizes a combination of carboxylic acid and sodium borohydride has been applied to carbazole giving an efficient 9-ethylation.¹⁰⁶ Also of preparative importance is the use of thallos ethoxide as base in dimethylformamide-ether: 9-methyl-, 9-ethyl-, *n*-propyl-, *n*-butyl-, benzyl-, and *n*-allylcarbazoles were efficiently produced, as well as 9,9'-dicarbazolylalkanes using C₃, C₄, and C₆ dihalides. 2-Acetyl- and 2-vinylcarbazole were also efficiently 9-ethylated by this route.¹⁰⁷ Another more recent approach to N-alkylation of carbazole utilizes potassium *tert*-butoxide in the presence of a catalytic quantity of 18-crown-6; 9-methylcarbazole was prepared in high yield.¹⁰⁸

It was known as long ago as 1923 that carbazole could be more simply alkylated by heating with potassium hydroxide than by the prior formation of the potassium salt. At that time it was shown that carbazole itself, as well as the more acidic 3-nitro- and 3-halocarbazoles could be N-methylated, N-ethylated, and N-*n*-propylated in acetone solution using

¹⁰⁰ A. N. Kost, M. A. Yurovskaya, T. V. Mel'nikova and O. I. Potanina, *Khim. Geterotsikl. Soedin.*, 207 (1973) [*CA* **78**, 136131m (1973)].

¹⁰¹ V. P. Lopatinskii, E. E. Sirotkina, and T. N. Zinchenko, *Tr. Tomsk. Gos. Univ., Ser. Khim.* **170**, 83 (1964) [*CA* **63**, 565h (1965)].

¹⁰² H. Hopff and H. Luessi, *Helv. Chim. Acta* **46**, 1052 (1963).

¹⁰³ Y. Tsunashima and M. Kuroki, *J. Heterocycl. Chem.* **18**, 315 (1981).

¹⁰⁴ Kh. Yu. Yuldashev, N. G. Sidorova, A. R. Abdurasuleva, K. N. Akhmedov, Kh. S. Tadjimukhamedov, I. A. Stemprevskaya, A. K. Abdushukurov, and A. Khaitbaeva, *Deposited Doc. VINITI* 7429 (1973) [*CA* **86**, 171030q (1971)].

¹⁰⁵ K. Yamasaki, I. Saito, and T. Matsuura, *Tetrahedron Lett.*, 313 (1975).

¹⁰⁶ G. W. Gribble, D. P. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).

¹⁰⁷ L. J. Kricka and A. Ledwith, *J. C. S. Perkin I*, 2292 (1972).

¹⁰⁸ W. C. Guida and D. J. Mathre, *J. Org. Chem.* **45**, 3172 (1980).

a strong aqueous solution of sodium hydroxide.¹⁰⁹ This and similar combinations have since been utilized: 3-aminocarbazole was converted to 3-amino-9-carboxymethylcarbazole¹¹⁰ using bromoacetic acid, and carbazole, 3-halocarbazoles, and 3,6-dihalocarbazoles were converted to their 9-(2-hydroxyethyl) derivatives^{111,112} using ethylene oxide. Carbazole itself was transformed into 9-*n*-hexyl, *n*-octyl-, *n*-decyl-, *n*-dodecyl-, *n*-tetradecyl and *n*-hexadecylcarbazoles,¹¹³ and into 9-(2-hydroxyethyl)carbazole (using 2-chloroethanol),¹¹⁴ and 9-(2-chloroethyl)carbazole (using the tosylate of 2-chloroethanol).⁹² 1,2-Di-(carbazol-9-yl)ethane was made using the ditosylate of 1,2-dihydroxyethane,¹¹⁵ 2-nitrocarbazole was converted to its 9-methyl, 9-ethyl, and 9-prop-1-yn-3-yl derivatives¹¹⁶ and 3-bromocarbazole to its 9-(2-chloroethyl) derivative using 2-chloroethanol tosylate.¹¹⁷ 3-Phenacetylcarbazole was 9-methylated by this method.¹¹⁸

The most straightforward and efficient method now available for N-alkylation of carbazoles is the "catalytic two-phase"¹¹⁹ process utilizing a benzene solution of the carbazole, 50% aqueous sodium hydroxide, and a catalytic quantity of a tetraalkylammonium salt (benzyltrimethylammonium chloride has been used) with the requisite halide.^{120,121} The efficient and simple formation of 9-methyl, 9-ethyl, 9-*n*-propyl, 9-*n*-butyl, and 9-benzyl derivatives has been described.¹²¹

2. Alkenyl

The interest in the polymerization¹⁰ of 9-ethenylcarbazole (37) (usually referred to as *N*-vinylcarbazole and abbreviated NVC) and related compounds has resulted in several methods for their preparation. The reaction

¹⁰⁹ T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, 2140 (1923).

¹¹⁰ S. I. Omel'chenko and Z. V. Pushkareva, *Zh. Obshch. Khim.* **28**, 2706 (1958) [*CA* **53**, 9184i (1959)].

¹¹¹ V. P. Lopatinskii, E. E. Sirotkina, and I. P. Zherebtsov, *Metody Poluch. Khim. Reakt. Prep.* **11**, 94 (1964) [*CA* **64**, 19542d (1966)].

¹¹² V. P. Lopatinskii, I. P. Zherebtsov, E. E. Sirotkina and S. K. Uereshchagina, *Izv. Tomsk. Politekh. Inst.* **136**, 11 (1965) [*CA* **65**, 8861a (1966)].

¹¹³ A. Hopfinger, J. Cislo, and E. Zielinska, *Rocz. Chem.* **42**, 823 (1968) [*CA* **70**, 3729a (1969)].

¹¹⁴ V. P. Lopatinskii, I. P. Zherebtsov, L. S. Alaberdina, and N. A. Khomyakova, *Izv. Tomsk. Politekh. Inst.* **198**, 79 (1974) [*CA* **83**, 58588c (1975)].

¹¹⁵ B. M. Vittimberga and M. L. Herz, *J. Org. Chem.* **35**, 3694 (1970).

¹¹⁶ E. Sawicki, *J. Am. Chem. Soc.* **75**, 4106 (1953).

¹¹⁷ J. Pielichowski and I. Kyzioł, *J. Polym. Sci., Polym. Lett. Ed.* **12**, 257 (1974).

¹¹⁸ D. A. Kinsley and S. G. P. Plant, *J. Chem. Soc.*, 1341 (1954).

¹¹⁹ M. Makasza, *Surv. Prog. Chem.* **9**, 1 (1980).

¹²⁰ A. Jonczyk and M. Makosza, *Rocz. Chem.* **49**, 1203 (1975) [*CA* **84**, 30793n (1976)].

¹²¹ H. Nishi, H. Kohno, and T. Kano, *Bull. Chem. Soc. Jpn.* **54**, 1897 (1981).

of carbazol-9-ylpotassium or -sodium generated from metal hydroxide with acetylene under pressure at ~ 145 to 190°C in a hydrocarbon solvent is the classic method¹²²; the use of a combination of acetylene and ethoxyethene under comparable conditions has also been described.¹²³ More recently, efficient preparations have been described that require only normal atmospheric pressure, thus reaction of carbazol-9-ylpotassium with acetylene in xylene in the presence of dimethyl sulfoxide was found to produce NVC in 95% yield,¹²⁴ and reaction at 150°C in dimethyl sulfoxide or 1-methylpyrrolidin-2-one using methyllithium, sodium hydride, or potassium hydroxide as base also gave good yields.¹²⁵

The trifluorovinyl analog **38** (Hal = F) could be obtained by reaction of carbazol-9-ylpotassium with tetrafluoroethene in tetrahydrofuran solution at room temperature¹²⁶ (cf. ref. 86). A complex mixture of products resulted from irradiation of carbazole in the presence of carbon tetrachloride; the inclusion of ethanol or water led to different products resulting from later interaction with these nucleophiles. In the absence of nucleophiles and in 3-methylpentane solution, 9-trichlorovinylcarbazole (**38**; Hal = Cl) was the main product.^{126a}

A different approach giving acceptable-to-good yields of NVC, and its 3,6-dihalo, 3,6-dialkyl, and 3,6-diacyl analogs, employed vinyl acetate and mercuric trifluoroacetate in trifluoroacetic acid at 95°C ¹²⁷ or mercuric acetate in acetone at 20°C ,¹²⁸ although the former workers state that **39** and **40** are formed when mercuric acetate is used as catalyst.¹²⁷

The reaction of carbazole with phenylacetylene in alkaline dimethyl sulfoxide gave the *Z*-alkene (**41**).¹²⁹ Reaction of carbazole with the acetals

¹²² W. Reppe and co-workers, *Justus Liebigs Ann. Chem.* **601**, 128 (1956); S. Otsuka and S. Murahashi, *Kogyo Kagaku Zasshi* **59**, 511 (1956) [*CA* **52**, 3818g (1958)]; O. Solomon, C. Ionescu, and I. Ciuta, *Chem. Tech. (Leipzig)* **9**, 202 (1957) [*CA* **51**, 15493e (1957)].

¹²³ T. Takizawa and K. Yonetani, *Mem. Inst. Sci. Ind. Res., Osaka Univ.* **5**, 110 (1947) [*CA* **47**, 2748i (1953)].

¹²⁴ Shansi University, *Hua Hsueh Tung Pao*, 21 (1977) [*CA* **87**, 134899e (1977)].

¹²⁵ S. R. Sandler, *Chem. Ind. (London)*, 134 (1973).

¹²⁶ A. Ya Yakubovich, A. P. Sergeev, and I. N. Belyaeva, *Dokl. Akad. Nauk SSSR* **161**, 1362 (1965) [*CA* **63**, 6967f (1965)]; I. N. Belyaeva U. V. Smolyanitskaya, P. O. Gitel, A. P. Sergeev, and A. Ya. Yakubovich, *Zh. Obshch. Khim.* **36**, 1793 (1966) [*CA* **66**, 85666g (1967)].

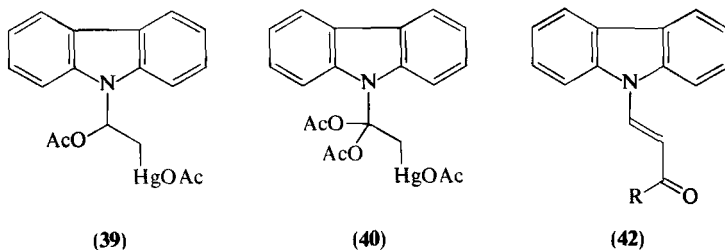
^{126a} B. Zelent and G. Durocher, *J. Org. Chem.* **46**, 1496 (1981); *Can. J. Chem.* **60**, 945 (1982).

¹²⁷ V. D. Filimonov, E. E. Sirotkina, and I. L. Gaibed, *Tezisy Dokl.—Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop., 2nd*, 1973, 138 (1973). [*CA* **86**, 16494a (1977)]; V. D. Filimonov, E. E. Sirotkina, and N. A. Tsekhanovskaya, *Zh. Org. Khim.* **15**, 174 (1979) [*CA* **90**, 186715y (1979)].

¹²⁸ V. P. Lopatinskii and E. E. Sirotkina, *Izv. Tomsk. Politekh. Inst.* **111**, 44(1961) [*CA* **57**, 16859e (1962)].

¹²⁹ V. D. Filimonov, *Khim. Geterotsikl. Soedin.*, 207 (1981) [*CA* **95**, 6043z (1981)].

$\text{MeCOCH}_2\text{CH}(\text{OMe})_2$ and $\text{EtOCH}=\text{CHCH}(\text{OEt})_2$, with sulfuric acid catalysis, gave **42**, ($\text{R} = \text{Me}$ and $\text{R} = \text{H}$, respectively). 1-Hydroxycarbazole behaved comparably, no interaction with the phenolic hydroxyl occurring.¹³⁰



3. Aryl and Heteroaryl

Although the preparation has been repeated,³² there have been no other reports of the type of reaction, (described in 1923) in which carbazole in the presence of excess potassium hydroxide and nitrobenzene at only 50°C gave a good yield of 9-(4-nitrophenyl)-carbazole, presumably via an adduct such as **43** subsequently oxidized by excess nitrobenzene and/or air.¹³¹ More recent examples of N-arylation of carbazoles have involved copper catalysis in reaction of aryl halides with carbazoles. Thus, copper bronze and potassium carbonate heated with the carbazole and the appropriate aromatic halide have produced 9-(4-methoxyphenyl)- and 9-(2-tolyl)carbazoles¹³²; 9-(4-phenylphenyl)carbazole, 1,4-di(carbazol-9-yl)benzene, 4,4'-di(carbazol-9-yl)biphenyl, and 9-(2-pyridyl)- and 9-(2-quinolyl)carbazoles¹³³; 9-[2-(2-phenylphenyl)phenyl]- and 9-[2-(4-methylphenyl)phenyl]carbazoles¹³⁴; 9-(3-bromo-6-nitrophenyl)-, 9-[3-(carbazol-9-yl)-], 9-(2-nitrophenyl)-, 9-(4-methyl-2-nitrophenyl)-, 9-(4-methoxycarbonyl)-1-nitro-, and 1-nitro-9-(4-tolyl)carbazoles¹³⁵; 9-(2-methoxycarbonylphenyl)carbazole¹³⁶; 9-[2-(2-nitrophenyl)phenyl]carbazole¹³⁷; and the stilbene **44**.¹³⁸ The combination copper(II) oxide with potassium carbonate and pyridine has yielded 9-(2-pyridyl)- and 9-(2-, 3-, and 4-nitrophenyl)carbazoles.¹³⁹ 9-(4-Dimethyl-

¹³⁰ H. J. Teuber, D. Cornelius, and H. Pfaff, *Chem. Ber.* **96**, 2617 (1963).

¹³¹ G. de Montmollin and M. de Montmollin, *Helv. Chim. Acta* **6**, 94 (1923).

¹³² M. Kuroki, *Nippon Kagaku Zasshi* **88**, 463 (1967) [*CA* **68**, 95187g (1968)].

¹³³ H. Gilman and J. B. Honeycutt, *J. Org. Chem.* **22**, 226 (1957).

¹³⁴ D. Hellwinkel and H. Seifert, *Justus Liebigs Ann. Chem.* **762**, 29 (1972).

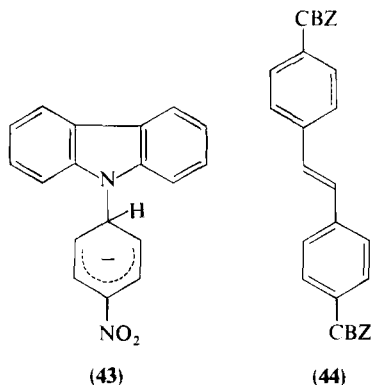
¹³⁵ C. Buchanan and S. H. Tucker, *J. Chem. Soc.*, 2750 (1958).

¹³⁶ R. Glaser, J. F. Blount, and K. Mislow, *J. Am. Chem. Soc.* **102**, 2777 (1980).

¹³⁷ D. Hellwinkel and H. Seifert, *Chem. Ber.* **105**, 880 (1972).

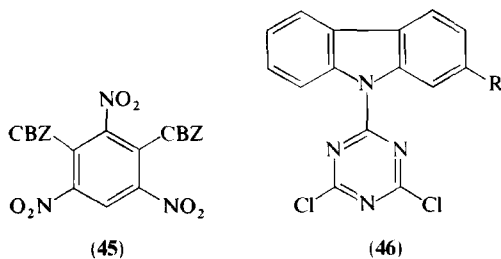
¹³⁸ G. Drefahl, G. B. Ploetner, and A. Ziegler, *Chem. Ber.* **95**, 2775 (1962).

¹³⁹ M. A. Khan and J. B. Polya, *J. Chem. Soc. C*, 85 (1970).



aminophenyl)carbazole was prepared by treating carbazole with copper(I) iodide and phenyllithium and then with 4-dimethylaminoiodobenzene.¹⁴⁰

Copper catalysis is not needed with more electrophilic aromatic and heteroaromatic halides; therefore, carbazole, 3,6-dichlorocarbazole and 3,6-dibromocarbazole for example, displaced fluoride and chloride from the 2,4-di- and 2,4,6-trinitrohalobenzenes in the presence of potassium hydroxide in dimethylformamide at room temperature.¹⁴¹ Both benzenoid chlorines were displaced in the reaction of 3,6-dichlorocarbazole with 2,6-dichloro-1,3,5-trinitrobenzene giving **45**.¹⁴¹ 2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride) reacted with carbazole and 2-nitrocarbazole even in the absence of added base, giving **46** (R = H and NO₂).¹⁴²



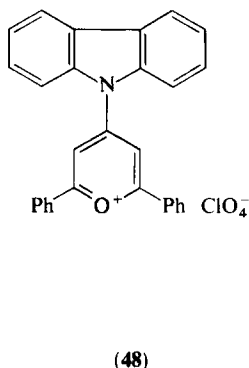
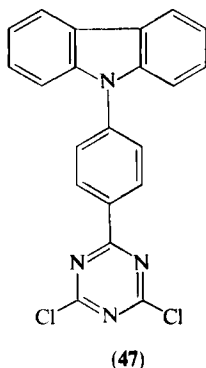
Rather strange results were obtained when cyanuric chloride was heated at 90 and 100°C, respectively, with 9-ethyl- and 9-phenylcarbazoles. A 1:1 mixture of N-substitution (presumably with loss of the original ethyl group) and C-substitution products were formed in very low yield from 9-ethylcarbazole and, also in very low yield, mainly **47** from 9-phenylcarbazole.¹⁴³

¹⁴⁰ O. Neunhoeffer and P. Heitmann, *Chem. Ber.* **94**, 2511 (1961).

¹⁴¹ G. P. Sharnin, V. S. Sergeev, and M. I. Shapshin, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **18**, 1519 (1975) [*CA* **84**, 74028w (1976)].

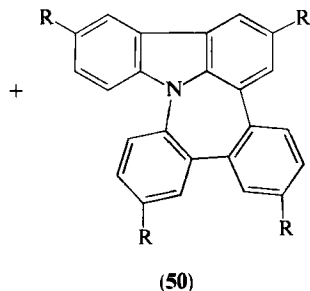
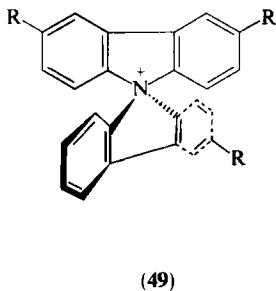
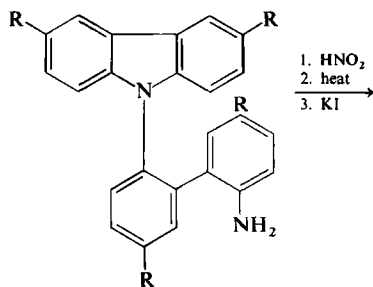
¹⁴² W. Schwarze, U.S. Patent 2,954,377 (1960) [*CA* **55**, P4548a (1961)].

¹⁴³ R. A. Shaw and P. Ward, *J. C. S. Perkin II*, 2075 (1973).



The interaction of 2,6-diphenyl-4-pyrone with carbazole and phosphorus oxychloride led interestingly to the pyrylium salt **48**.¹⁴⁴ The formation of 9-phenylcarbazole by addition of carbazol-9-yllithium to benzyne has been recorded.¹⁴⁵

Unique in carbazole chemistry is a paper describing the formation of isolable spirocyclic salts with the "carbazole" nitrogen having a valence of four. Although these salts no longer have 14 π -electron systems, these reactions are included here because the formation of such spiro cells salts as **49**



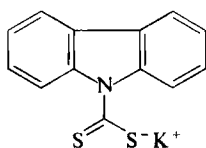
¹⁴⁴ J. Van Allan and G. Reynolds, *J. Heterocycl. Chem.* **13**, 73 (1976).

¹⁴⁵ F. M. Stoyanovich and M. A. Marakatkina, *Zh. Org. Khim.* **16**, 2251 (1980) [*CA* **94**, 64781d (1981)].

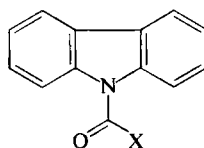
(R = H or Me) is formally a carbazole N-arylation. The ring closure was effected by diazotization and heating. Minor products in these processes were the dibenz [4,5:6,7]azepino[1,2,3-*jk*]carbazoles (50).¹³⁷

4. Acyl and Related Groups

The preformation of carbazol-9-ylpotassium (sodium) has been much less used for the introduction of acyl groups onto nitrogen: examples are the formation of 9-methoxy- and 9-ethoxy-carbonylcarbazoles,¹⁴⁶ the dithio-carbamate salt 51,¹⁴⁷ and the malonate 52¹⁴⁸ by reaction with the alkoxy-chloroformates, carbon disulfide, and malonic acid half-acid chloride, respectively.



(51)

(52) X = CH₂COOH(55) X = CH₃S(56) X = NH₂

The early use of aqueous potassium hydroxide in acetone for the acetylation and benzoylation of 3-nitrocarbazole using the acid chlorides¹⁰⁹ has been subsequently repeated for the N-acetylation of 3,6-dinitrocarbazole with acetic anhydride,¹⁴⁹ for the N-acetylation, ethoxycarbonylation, 4-fluorobenzoylation, and prop-2-ynoylation of 2-nitrocarbazole¹¹⁶ and for the methoxy- and ethoxycarbonylation¹⁵⁰ of carbazole itself utilizing the chloroformate esters.

Some use has been made of the N-Grignard derivative of carbazole: phenylacetyl (from the acid chloride),¹¹⁸ ethoxycarbonylcarbonyl,¹⁵¹ acetyl and 5-bromopent-4-enoyl,¹⁵² and various α -aminoacyl derivatives,¹⁵³ (all

¹⁴⁶ R. P. Lastovskii, U.S.S.R. Patent 118,503 (1959) [CA 53, P22016d (1959)].

¹⁴⁷ R. D. Bereman and D. Nalewajek, *Inorg. Chem.* **17**, 1085 (1978); A. S. Safaev, A. K. Kadyrov, D. V. Islamova, and Sh. Isamokhamedova, *Tr. Tashk. Politekh. Inst.* **107**, 229 (1973) [CA 83, 61117d (1975)].

¹⁴⁸ G. Wittig and P. Hornberger, *Justus Liebigs Ann. Chem.* **577**, 11 (1952).

¹⁴⁹ R. Oda, Z. Yoshida, and Y. Kato, *J. Chem. Soc. Jpn., Ind. Chem. Sect.* **55**, 239, 285, 655, 656 (1952) [CA 47, 12283a (1953)]; Z. Yoshida, *ibid.* **57**, 238 (1954) [CA 49, 11620g (1955)].

¹⁵⁰ M. A. Fletcher, M. W. Lakin, and S. G. P. Plant, *J. Chem. Soc.*, 3898 (1953).

¹⁵¹ I. I. Lapkin and Yu. P. Dormidonotov, *Uch. Zap.—Permsk. Gos. Univ. im. A. M. Gor'kogo* **229**, 243 (1970) [CA 77, 164370m (1972)].

¹⁵² E. A. Parfenov and A. M. Yurkevich, *Zh. Org. Khim.* **7**, 2471 (1971) [CA 76, 853232 (1972)].

¹⁵³ L. Birkofer and E. Frankus, *Chem. Ber.* **94**, 216 (1961).

from the corresponding ethyl esters) were made in this way. Thallous ethoxide in dimethylformamide-ether was utilized for the preparation of 9-acetylcarbazole using vinyl acetate as an electrophile¹⁵⁴; the use of aqueous potassium hydroxide and acetone had led to 9-(1-acetoxyethyl)carbazole. 9-Cyanocarbazole was prepared using sodium hydride and cyanogen bromide.¹⁵⁵ Irradiation of carbazole in the presence of carbon tetrachloride and ammonia gave 9-cyanocarbazole and the 9,9'-dimer.^{126a}

For 9-acylations, however, it is usually unnecessary to preform an anion. Direct electrophilic attack at carbazole nitrogen can occur (see Section II,A,4) followed by loss of the N-proton to produce *N*-acylcarbazoles conveniently.

Several catalysts have been recommended for the *N*-acetylation of carbazole with acetic anhydride: boron trifluoride,⁶¹ phosphorus pentoxide,¹⁵⁶ concentrated sulfuric acid,¹⁵⁷ zinc chloride,¹⁵⁸ and phosphoric acid¹⁵⁸ all gave 9-acetylcarbazole in moderate to good yield. 9-Acetylcarbazole can also be prepared using the Vilsmeier complex of *N,N*-dimethylacetamide and phosgene.⁶⁷

2-Chloroacetyl chloride¹⁵⁹ and 2-bromoacetyl bromide⁶² *N*-acylated without a catalyst but 2-chloroacetic anhydride required concentrated sulfuric acid.¹⁶⁰ 3-Chloro-¹⁶¹ and 3-bromopropionyl¹⁶² chlorides 9-acylated without a catalyst as did cinnamoyl chloride¹⁴⁸ and phosgene, the last producing 9-chloroformylcarbazole.¹⁶³

The general picture emerging is that acid chlorides are sufficiently electrophilic to *N*-acylate carbazole directly but that acid anhydrides require a Lewis acid or protonic acid catalyst. Direct and efficient *N*-trifluoroacetylation with trifluoroacetic anhydride nicely illustrates the balance, this more reactive anhydride requiring no catalyst.⁶⁸

The dichloroacetal **53** *N*-acylated carbazole in the presence of stannic chloride producing **54**,¹⁶⁴ and trichloromethylthiomethane led to the thio-carbamate **55** on reaction catalyzed by zinc chloride.¹⁶⁵ Carbazole reacts

¹⁵⁴ L. J. Kricka and A. Ledwith, *J. Org. Chem.* **38**, 2240 (1973).

¹⁵⁵ C. Wentrup, *Tetrahedron* **27**, 367 (1971).

¹⁵⁶ A. V. Spasov and A. Aleksiev, *Z. Chem.* **14**, 58 (1974).

¹⁵⁷ E. Funakubo, T. Genma, and T. Takahashi, *Technol. Reps. Osaka Univ.* **12**, 177 (1962) [*CA* **58**, 4500g (1962)].

¹⁵⁸ V. P. Lopatinskii, E. E. Sirotkina, and M. M. Anosova, *Izv. Tomsk. Politekh. Inst.* **111**, 36 (1961) [*CA* **58**, 2422c (1963)].

¹⁵⁹ R. Dahlbom, *Acta Chem. Scand.* **6**, 309 (1952).

¹⁶⁰ V. Hach and M. Protiva, *Chem. Listy* **47**, 729 (1953).

¹⁶¹ J. Heller and C. B. Kingsley, *Makromol. Chem.* **78**, 47 (1964).

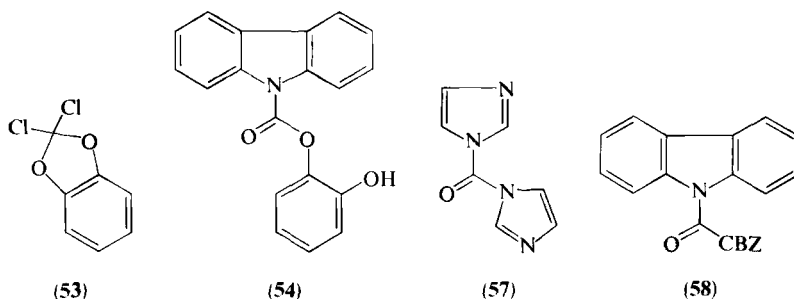
¹⁶² I. O. Hromatka and H. Schramek, *Monatsh. Chem.* **92**, 1252 (1961).

¹⁶³ A. W. Weston, R. W. DeNet, and R. J. Michaels, *J. Am. Chem. Soc.* **75**, 4006 (1953).

¹⁶⁴ H. Gross, J. Rusche, and M. Mirsch, *Chem. Ber.* **96**, 1382 (1963).

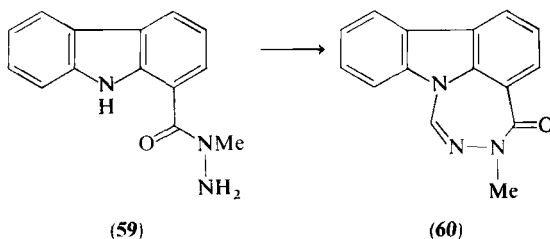
¹⁶⁵ H. Gross and G. Matthey, *Chem. Ber.* **97**, 2606 (1964).

with urea on heating in aniline to give the substituted urea **56**¹⁶⁶ and with the phosgene equivalent **57** in hot dimethyl sulfoxide to give the fully substituted urea **58**.¹⁶⁷



Ketene in the presence of methanesulfonic acid is yet another means for the preparation of 9-acetylcarbazole,¹⁶⁸ whereas the use of diketene leads to 9-acetoacetylcarbazole.¹⁶⁹

Treatment of the hydrazide **59** with ethyl orthoformate causes an intramolecular N-acylation resulting in the tetracycle **60**.¹⁷⁰ The conversion of 1,4-diphenylcarbazole into **61** using *N*-methylformanilide-phosphorus oxychloride at 95°C must involve an oxidation at some stage.¹⁷¹ Heating carbazole with diphenyl 2-benzylmalonate, diethyl 2-ethylmalonate, or malonic acid-phosphorus oxychloride produced the tetracycles **62** (R = PhCH₂, Et, and H, respectively).^{172,173} It is not clear whether the N-9 or the C-1 acylations required for the formation of **62** occur first, although it is likely that the initial attack is at the nitrogen.



¹⁶⁶ V. P. Lopatinskii and V. V. Gol'dshtein, *Izv. Tomsk. Politekh. Inst.* **185**, 127 (1970) [*CA* **75**, 63541w (1971)].

¹⁶⁷ J. Bergman, R. Carlsson, and B. Sjöberg, *J. Heterocycl. Chem.* **14**, 1123 (1977).

¹⁶⁸ M. N. Modi, N. S. Ramegowda, A. K. Koul, C. K. Narang, and N. K. Mathur, *Indian J. Chem.* **11**, 1049 (1973).

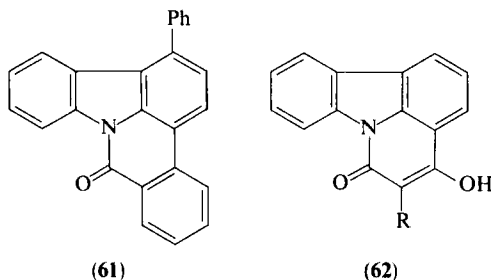
¹⁶⁹ V. V. Perakalin and O. M. Lerner, *Zh. Obshch. Khim.* **21**, 1995 (1951) [*CA* **46**, 8115h (1952)].

¹⁷⁰ N. P. Peet and S. Sunder, *J. Heterocycl. Chem.* **14**, 1147 (1977).

¹⁷¹ T. Teitei, *Aust. J. Chem.* **23**, 185 (1970).

¹⁷² E. Ziegler, H. Junek, and U. Rossmann, *Monatsh. Chem.* **92**, 809 (1961).

¹⁷³ M. Harfenist, *J. Org. Chem.* **27**, 4326 (1962).



5. Oxy-, Amino-, and Thioalkyl

9-Hydroxymethylcarbazole (**63**: $R^1 = R^2 = H$) and its 3,6-dichloro analog have been prepared by reaction of the carbazole with formaldehyde in aqueous ammonia^{174,175} and **63** ($R^1 = R^2 = H$), and the 3-methyl, 3,6-dimethyl, 3-bromo, 3,6-dibromo, and 3-chloro analogs have been prepared using paraformaldehyde and 5% potassium hydroxide in butanol-toluene.¹⁷⁶ The methyl ether **63** ($R^1 = Me$, $R^2 = H$) was prepared by 9-alkylation of carbazole with chloromethyl ether using sodium amide in liquid ammonia.¹⁶ Generally, 9-(1-alkoxyalkyl)carbazoles are available (1) from the interaction of an enol ether with carbazole alone.¹⁷⁷ Or utilizing mercuric sulfate-sulfuric acid catalysis¹⁷⁸ (**63**: $R^1 = n\text{-Bu}$, $R^2 = Me$ and $R^1 = Et$, $R^2 = Me$ were thus prepared); or (2) from aldehyde, alcohol, and strong acid, as in the formation of a large range of **63s** in which $R^1 = Me$, Et , $n\text{-octyl}$, $n\text{-propyl}$, isopropyl, *tert*-butyl, and $n\text{-pentyl}$, and $R^2 = H$, Me , Et , $n\text{-propyl}$, and isopropyl and in which the 3-methyl, chloro, bromo, nitro, and 3,6-dichloro analogs were also prepared.¹⁷⁹ Dicarbazole ethers (**64**: $R = Me$ or Et) can result in some cases.¹⁸⁰ A more complex type of 9-alkoxyalkylcarbazole (**65**) is the result of fusing the heterocycle with 1,2,3,5-tetra-*O*-acetyl- β -D-ribofuranose.¹⁸¹

¹⁷⁴ E. G. Novikov, T. F. Aksenova, and A. M. Belyaeva, *Koks Khim.* 39 (1965) [*CA* 63, 16536d (1965)].

¹⁷⁵ E. Zielinska, A. Hopfinger, and J. Gutowski, *Rocz. Chem.* 43, 1283 (1969) [*CA* 71, 124109c (1969)].

¹⁷⁶ J. Ormran and M. Zander, *Chem. Ber.* 103, 3356 (1970).

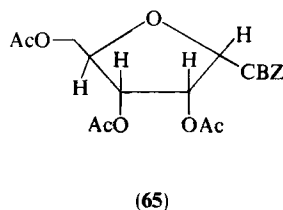
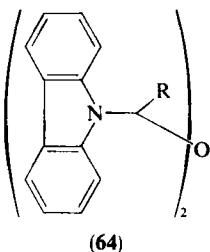
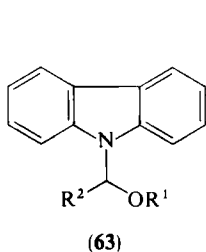
¹⁷⁷ J. Furukawa, A. Onishi, and T. Tsuruta, *J. Org. Chem.* 23, 672 (1958).

¹⁷⁸ V. P. Lopatinskii, E. E. Sirotkina, and A. W. Yushko, *Izv. Tomsk. Politekh. Inst.* 148, 67 (1967) [*CA* 71, 21973a (1969)].

¹⁷⁹ V. A. Anfinogenov, V. D. Filiminov, and E. E. Sirotkina, *Zh. Org. Khim.* 14, 1723 (1978) [*CA* 90, 38764y (1979)]; E. E. Sirotkina, V. A. Anfinogenov, V. D. Filiminov, M. F. Tavobilov, and A. K. Svetlov, USSR Patent 687,072 [*CA* 92, P41759x (1980)].

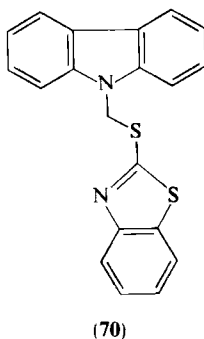
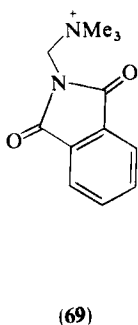
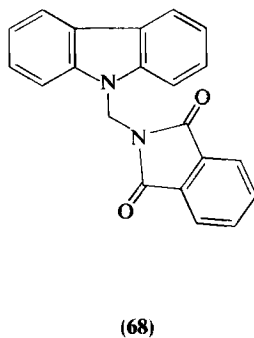
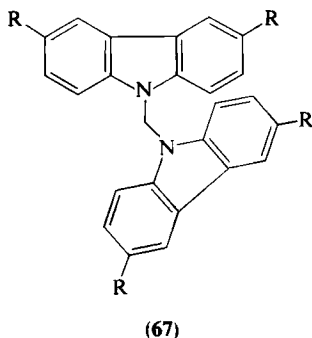
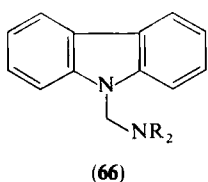
¹⁸⁰ E. E. Sirotkina, V. D. Filimonov, and V. A. Anfinogenov, *Izv. Tomsk. Politekh. Inst.* 272, 77 (1975).

¹⁸¹ C. Chavis, F. Dumont, G. Gosselin, and J. L. Imbach, *Carbohydr. Res.* 46, 43 (1976).



9-(1-Acetoxyethyl)carbazoles are formed from carbazole and 3-chloro-carbazole when treated with vinyl acetate and potassium hydroxide in acetone¹⁸² (cf. Section II,B,4 and ref. 154).

Carbazole undergoes a Mannich-type condensation at the nitrogen under mild conditions with formaldehyde and amine in ethanol; in this way **66** [R = Me, Et, (CH₂)₂O(CH₂)₂, and CH₂CH₂Cl] were prepared.^{183,184} An



¹⁸² V. P. Lopatinskii and Yu. P. Shekhirev, *Izv. Tomsk. Politekh. Inst.* **136**, 162 (1965) [*CA* **65**, 16930f (1966)]; V. P. Lopatinskii, Yu. P. Shekhirev, V. M. Sutyagin, and E. A. Danilova, *ibid.* **163**, 28 (1970) [*CA* **75**, 118194t (1971)].

¹⁸³ H. Hellmann and I. Löschmann, *Chem. Ber.* **87**, 1684 (1954).

¹⁸⁴ R. C. Elderfield and J. R. Wood, *J. Org. Chem.* **27**, 2463 (1962).

interesting contrast emerged when 2-acetylcarbazole and 3,6-diacetylcarbazole were subjected to the "normal" Mannich conditions, that is, using the amine hydrochloride: condensation occurred at the methyl group, but under the "mild" nonacidic conditions described above, condensation occurred at the nitrogen.¹⁸⁵ The implication clearly is that the N-condensation processes proceed in each case via an equilibrium concentration of the carbazol-9-yl anion.

Formaldehyde and acetic acid convert carbazole and the 3,6-dihalocarbazoles to the 9,9'-dicarbazolylmethanes **67** (R = H or Hal).^{186,187} The phthalimidomethyl group can be introduced onto the carbazole nitrogen, giving **68** by reaction with phthalimide-formaldehyde in ethanol,¹⁸⁸ or more elaborately by reacting carbazol-9-ylpotassium with the salt **69** in dimethylformamide.¹⁸⁹

The 9-heteroarylthiomethyl derivative **70** was prepared by a comparable process utilizing silver nitrate to catalyze the reaction between carbazole, formaldehyde, and the benzthiazole thiol.¹⁹⁰

6. Nitrogen

The N-nitrosation of carbazoles is a well-established process, several more examples of which have been described^{50,55,191-194}; sodium nitrite in acetic acid is the most frequently used reagent.

Carbazole oxidized by nickel peroxide in the absence of light and in the presence of 2-methyl-2-nitrosopropane gave the radical **71**,¹⁹⁵ an observation taken as additional evidence for the intermediacy of radical cations, trapped in this case by the nitrosoalkane, in oxidative dimerization of carbazoles (see Section II,A,2).

¹⁸⁵ E. Hannig and B. Schobess, *Arch. Pharm. (Weinheim, Ger.)* **296**, 536 (1963).

¹⁸⁶ P. Bruck, *J. Org. Chem.* **35**, 2222 (1970).

¹⁸⁷ F. Mužík and Z. J. Allan, *Collect. Czech. Chem. Commun.* **22**, 641 (1957).

¹⁸⁸ M. B. Winstead and H. W. Heine, *J. Am. Chem. Soc.* **77**, 1913 (1955).

¹⁸⁹ H. Hellmann and I. Löschmann, *Chem. Ber.* **87**, 1690 (1954).

¹⁹⁰ Zh. G. Saidaliev, A. Kadyrov, and A. Safaev, *Deposited Doc. VINITI* 752 (1974) [*CA* **86**, 171312h (1977)].

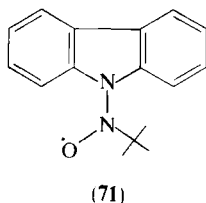
¹⁹¹ V. I. Shishkina, S. I. Omel'chenko, and V. A. Soshin, *Tr. Ural. Politekh. Inst. im. S. M. Kirova* **96**, 19 (1960) [*CA* **55**, 24715c (1961)].

¹⁹² N. L. Drake, H. J. S. Winkler, C. M. Kraebel, and T. D. Smith, *J. Org. Chem.* **27**, 1026 (1962).

¹⁹³ C. I. Simonescu and V. Percec, *J. Polym. Sci., Polym. Chem. Ed.* **17**, 2287 (1979).

¹⁹⁴ J. Kyziol and J. Tarnawski, *Rev. Roum. Chim.* **25**, 721 (1980) [*CA* **94**, 83877f (1981)].

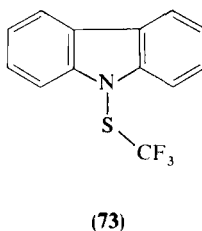
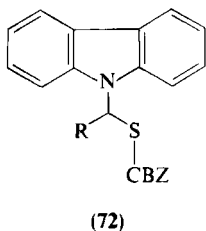
¹⁹⁵ S. Terabe and R. Konaka, *J. Am. Chem. Soc.* **91**, 5655 (1969).



7. Sulfur

Carbazole has been converted to 9-tosyl¹⁹⁶ and 9-methanesulfonyl¹⁹⁷ derivatives using aqueous sodium hydroxide and acetone and pyridine, respectively. A phenylsulfonylation of 3-methylcarbazole utilized potassium *tert*-butoxide in dimethylformamide,¹⁹⁸ whereas the mesylation and tosylation of 2-nitrocarbazole were carried out with strong aqueous potassium hydroxide in acetone.¹¹⁶ The best way to phenylsulfonylate carbazole is to use the catalytic two-phase procedure.^{119,199}

Although α -chloromethyl²⁰⁰ and -ethylsulfur chloride²⁰¹ reacted with a mol equivalent of carbazole at each electrophilic site giving **72** (R = H and Me),²⁰² trifluoromethylsulfur chloride would react only with the Grignard derivative of carbazole, giving **73**.²⁰²



Substitution at carbazole nitrogen and the formation of **74**, presumably via a radical cation, resulted from reaction with the cation radical salt **75** in acetonitrile.²⁰³

¹⁹⁶ D. Klamann and H. Bertsch, *Chem. Ber.* **89**, 2007 (1956).

¹⁹⁷ J. L. Huppertz and W. H. F. Sasse, *Aust. J. Chem.* **17**, 1406 (1964).

¹⁹⁸ M. T. Goetz, *J. Heterocycl. Chem.* **11**, 445 (1974).

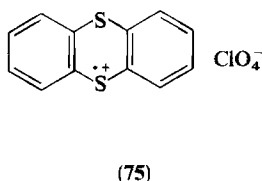
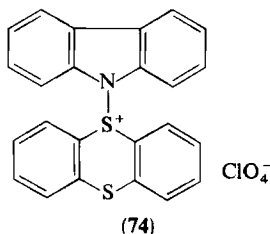
¹⁹⁹ A. Hammam and J. A. Joule, unpublished observations.

²⁰⁰ H. Brintzinger, H. Schmah, and H. Witte, *Chem. Ber.* **85**, 338 (1952).

²⁰¹ H. Brintzinger and H. Ellwanger, *Chem. Ber.* **87**, 300 (1954).

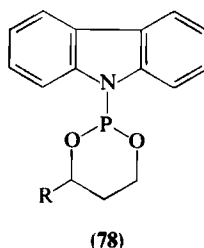
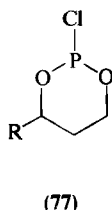
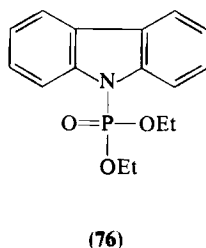
²⁰² A. Haas and V. Niemann, *Chem. Ber.* **110**, 67 (1977).

²⁰³ K. Kim and H. J. Shine, *J. Org. Chem.* **39**, 2537 (1974).



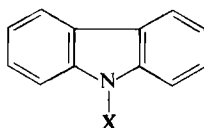
8. Phosphorus

Although carbazole itself will not react with diethylphosphoryl chloride, its potassium salt yields **76**.²⁰⁴ The cyclic chlorophosphites **77** (R = H and Me) reacted without prior conversion of carbazole to its salt, giving **78** (R = H and Me).²⁰⁵



9. Boron

The N-Grignard derivative of carbazole reacts with boron trifluoride to give tricarbazol-9-ylborine,²⁰⁶ while ethyl diborane at 90°C gave mainly carbazol-9-yl-diethylborine (**79**).²⁰⁷



(79) X = BEt₂
 (80) X = AlH₂ · NMe₃

²⁰⁴ B. P. Lugovkin and B. A. Arbuzov, *Zh. Obshch. Khim.* **22**, 2041 (1952) [*CA* **47**, 9283h (1953)]; B. A. Arbuzov and V. M. Zoroastrova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 104 (1966) [*CA* **64**, 12631f (1966)].

²⁰⁵ E. E. Nifant'ev, N. L. Ivanova, and D. A. Predvoditelev, *Dokl. Akad. Nauk SSSR* **228**, 357 (1976) [*CA* **85**, 94327s (1976)].

²⁰⁶ A. Dornow and H. H. Gehrt, *Angew. Chem.* **68**, 619 (1956).

²⁰⁷ H. Bellut and R. Koester, *Justus Liebigs Ann. Chem.* **738**, 86 (1970).

10. Aluminium

The aluminium hydride-trimethylamine complex releases hydrogen by reaction with carbazole giving the complex **80**.²⁰⁸

C. REACTIONS INVOLVING N-SUBSTITUENTS

1. Alkyl

With few exceptions, the reactions of functional groups separated by a chain of two or more saturated atoms from carbazole nitrogen show no deviation from their normal behavior.

Methyl, ethyl, and benzyl groups can be removed from carbazole nitrogen by heating with sulfur at 300°C.^{209,210} C-Alkyl groups are unaffected, although a 3-formyl group was lost and a 3-acetyl group partly lost during such treatment. A benzyl group was cleaved, although only in moderate yield, by lithium in refluxing tetrahydrofuran,²¹¹ and it was also removed by *N*-bromosuccinimide in the presence of dibenzoyl peroxide, although partial 3-bromination of the carbazole also resulted.²¹²

There are several examples of the 1,2-elimination of hydrogen chloride from 9-(2-chloroethyl)carbazoles, using potassium hydroxide in ethanol, generating the 9-vinylcarbazoles.^{63,92} 3-Dimethylamino-9-(2-hydroxyethyl) carbazole comparably lost water on base treatment.⁹² Dimethylamine displacement of halogen, then amine *N*-oxide formation and elimination was utilized to produce 9-alkenylcarbazoles with four, five, and six carbon atoms from the corresponding ω -haloalkyl carbazoles.⁷⁸

9-(2-Hydroxyethyl)carbazole can be oxidized with copper(II) oxide-potassium hydroxide at 240°C to the carbazol-9-ylacetic acid²¹³; the benzoate ester of the alcohol was cleaved to regenerate alcohol using phenyl Grignard reagent.²¹⁴ The 9-acetic acid is also produced by alkaline hydrolysis of the corresponding nitrile.²¹⁵

²⁰⁸ W. Marconi, A. Mazzei, F. Bonati, and M. de Malde, *Gazz. Chim. Ital.* **92**, 1062 (1962).

²⁰⁹ Ng. Ph. Buu-Hoi and G. Saint-Ruf, *J. Chem. Soc. C*, 924 (1966).

²¹⁰ J. C. Perche, G. Saint-Ruf, and Ng. Ph. Buu-Hoi, *J. C. S. Perkin Trans. I*, 260 (1972).

²¹¹ H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.* **80**, 380 (1958).

²¹² M. Okawara, H. Sato, and E. Imoto, *Kogyo Kagaku Zasshi* **60**, 1146 (1957) [*CA* **53**, 14979b (1959)].

²¹³ I. P. Zhrebtsov and V. P. Lopatinskii, *Izv. Tomsk. Politekh. Inst.* **198**, 70 (1974) [*CA* **83**, 58586a (1975)].

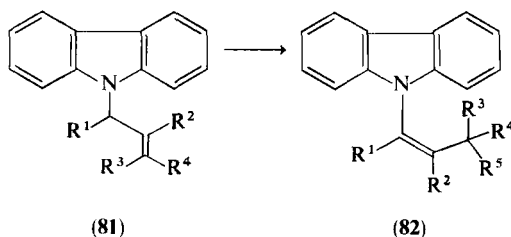
²¹⁴ K. G. Mizuch, N. M. Kasatkin, and Ts. M. Gel'fer, *Zh. Obshch. Khim.* **27**, 189 (1957) [*CA* **51**, 12885d (1957)].

²¹⁵ Z. V. Pushkareva, M. K. Murshtein and L. A. Stepanova, *Sb. Nauchn. Tr. Khim. Sverdlovsk. Insk. Nar. Khoz.*, 74 (1971) [*CA* **78**, 111056c (1973)].

A special reaction is the oxidation of 1,2-di(carbazol-9-yl)ethane with air at 188°C in the presence of di-*tert*-butyl peroxide forming 1,2-di(carbazol-9-yl)ethene.¹¹⁵ The same material was obtained from di-*tert*-butyl peroxide initiated decarbonylation of carbazol-9-ylethanal in the absence of air; with air present, 9-methylcarbazole, dicarbazol-9-ylmethane, and polymer resulted.¹¹⁵

9-Allylcarbazole (and 3-chloro- and 3-chloro-6-nitroanalogs) hydroxylate, normally with permanganate^{115,216}, the diol from 9-allylcarbazole cleaved normally with periodate.¹¹⁵

The double bond of 9-allylcarbazoles can be moved into conjugation with the nitrogen by treatment with potassium *tert*-butoxide in dimethyl sulfide; the *cis*-prop-1-enyl isomers were formed initially in studies with 9-allyl-carbazole, 9-allyl-3-chlorocarbazole, 9-allyl-3-nitrocarbazole, and 9-allyl-3,6-dichlorocarbazole.²¹⁷ Such isomerizations must proceed via a carbanion produced by proton abstraction from the saturated carbon on nitrogen. Indeed, when the red anion from 9-benzylcarbazole, formed using *n*-butyllithium, was quenched with deuterium oxide, the 9-CHDPh derivative was obtained.²¹⁸ When the anions from 9-allyl-carbazoles in the series **81** ($R^1 = R^2 = R^3 = R^4 = H$; $R^1 = Me$, $R^2 = R^3 = R^4 = H$; $R^1 = R^3 = R^4 = H$, $R^2 = Me$; $R^1 = R^2 = R^4 = H$, $R^3 = Me$; and $R^1 = R^2 = H$, $R^3 = R^4 = Me$) were reacted with the carbon electrophiles *n*-butyl, isopropyl and benzyl bromides,²¹⁹ and isobutenyl chloride,¹⁹ in each case the alkylating agent attacked mainly at the carbon remote from the nitrogen, thus giving the conjugated product **82** ($R^5 = \text{electrophile}$) with the double bond *cis*.^{19,219} Ethoxide-catalyzed isomerization of **83** converted it to **84**.²²⁰



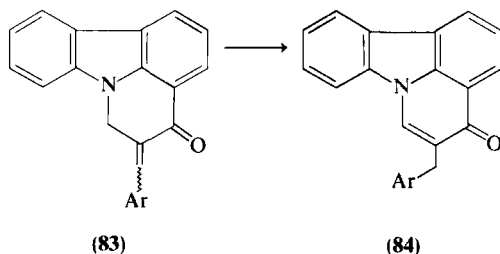
²¹⁶ I. P. Zharebtsov, V. P. Lopatinskii, N. M. Rovkina, and I. N. Mordvinova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **23**, 968 (1980) [*CA* **94**, 47066g (1981)].

²¹⁷ V. D. Filimonov, S. G. Gorbachev, and E. E. Sirotkina, *Khim. Geterotsikl. Soedin.*, 340 (1980) [*CA* **93**, 71458m (1980)]; S. G. Gorbachev, *Miner. Syr'e Neftekhim.*, 163 (1977) [*CA* **92**, 198209r (1980)].

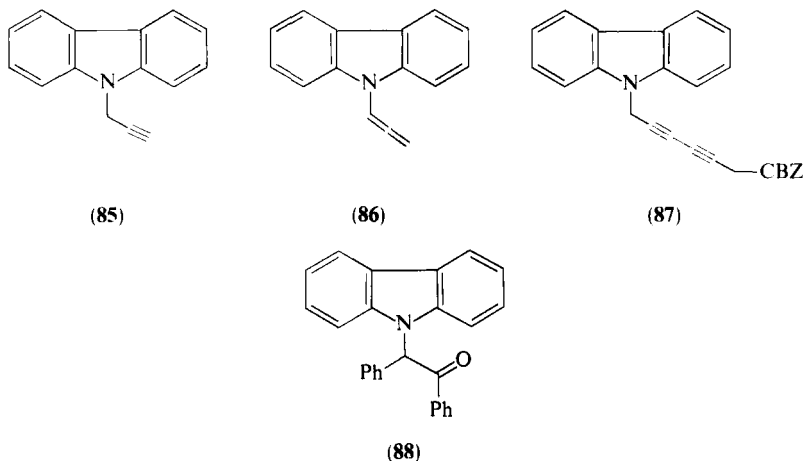
²¹⁸ J. J. Eisch and C. A. Kovacs, *J. Organomet. Chem.* **30**, C97 (1971).

²¹⁹ M. Julia, A. Schouteeten, and M. Baillarge, *Tetrahedron Lett.*, 3433 (1974).

²²⁰ H. Rapoport and D. M. Bowman, *J. Org. Chem.* **24**, 324 (1959).



Equilibration of the alkyne **85** with potassium hydroxide alone produced a 1:1 mixture of allene **86** and starting material; complete conversion to **86** resulted from treatment with potassium hydroxide or potassium *tert*-butoxide in dimethyl sulfoxide.^{90,96}



The alkyne **85** has been oxidatively dimerized with copper(I) salts giving **87**,^{79,91} and coupled with 1-bromo-2-phenylethyne in the presence of copper (II) salts.²²¹ The 9-phenacylcarbazole **88** was cleaved to 9-benzylcarbazole with strong aqueous alkali in hot glycol.²²²

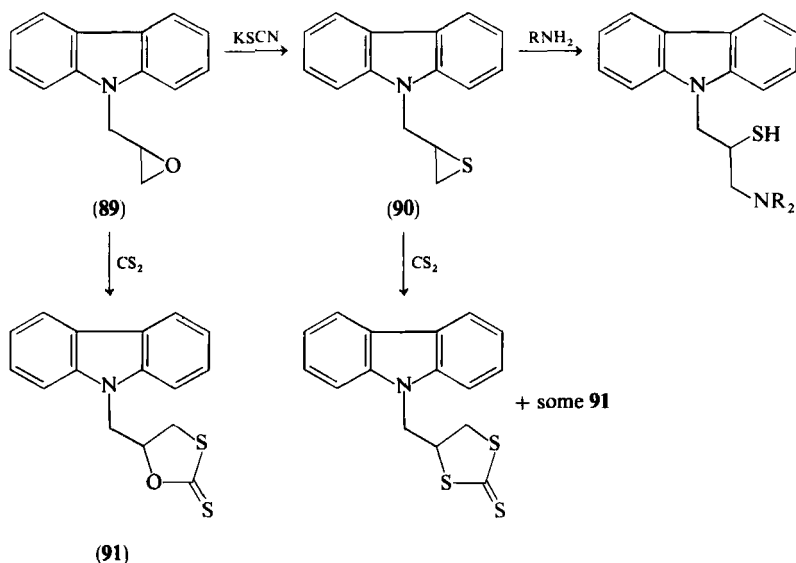
Entirely typical epoxide and thioepoxide reactions were shown by **89** and **90** and are summarized in the following formulas.^{223,224}

²²¹ J. L. Dumont, A. Metge, W. Chodkiewicz, and P. Cadiot, *C. R. Hebd. Seances Acad. Sci., Ser. C* **260**, 215 (1965).

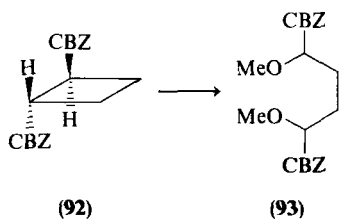
²²² N. L. Allinger and B. A. Youngdale, *J. Org. Chem.* **24**, 306 (1959).

²²³ V. A. Mullin, A. N. Zdotov, and V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **23**, 288 (1980) [*CA* **93**, 114245j (1980)].

²²⁴ V. A. Mullin, A. N. Zolotov, and V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **23**, 41 (1980) [*CA* **93**, 7939s (1980)].



The head-to-head trans-cyclorimer **92** of 9-vinylcarbazole (see Section II,C,2) undergoes C—C bond fission by a one-electron oxidative process on treatment with cerium ammonium nitrate or tris-(*p*-bromophenyl)ammonium hexachloroantimonate in methanol giving **93**.²²⁵



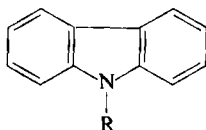
2. Alkenyl

Aqueous acid has been utilized to cleave the enamine-like C—N bond of the 9-alkenylcarbazoles **94**¹²⁹ and **95**¹³⁰ and the products **82** of alkylation of the anions of 9-allylcarbazoles²¹⁹; hydrated ferric nitrate was used to remove the vinyl group from 3-halo-9-vinylcarbazoles.²²⁶ Strong base

²²⁵ A. Ledwith, P. Beresford, and M. C. Lambert, *J. Chem. Soc. C*, 2508 (1970).

²²⁶ J. Pielichowski and M. Olszanska, *Pol. J. Chem.* **52**, 1089 (1978) [*CA* **89**, 163337s (1978)].

deprotonation of 9-alkenylcarbazoles produced the same carbanion as that available from their allyl isomers²²⁷ (see Section II,C,1).



(94) R = CH=CHPh (cis)

(95) R = CH=CHCOMe (trans)

(96) R = CH₂CH₂SnPh₃

Electrophilic addition to 9-vinylcarbazole occurs in the Markovnikov sense, thus hydrogen chloride,²²⁸ hydrogen bromide,²²⁸ chlorine, and bromine in carbon tetrachloride,^{229,230} and iodine chloride in pyridine²³¹ are recorded as adding with initial electrophilic attack at the methylene. Mercuric acetate in methanol gave 9-(2-acetoxymercuri-1-methoxyethyl)carbazole.²³² Although 9-vinylcarbazole gave an iodohydrin, comparable reaction with methanolic sodium hypochlorite led to 9-(2-chlorovinyl)carbazole.²³³ Catalytic reduction of the latter produced 9-(2-chloroethyl)carbazole.²³³ Triphenyltin hydride gave 96.²³⁴

A subsequent elimination of hydrogen halide prompted by the lability of halogen on the carbon attached to nitrogen, a second halogen addition, and a repetition of the cycle must account for the reported formation of 9-pentachloro- and 9-pentabromoethylcarbazoles on reaction with excess halogen in methanol and acetic acid, respectively.²³⁰ Addition of bromine to *N*-vinylcarbazole in benzene as solvent was accompanied by 3,6-dibromination; in ethanol, 3,6-dibromo-9-(2-bromo-1-ethoxyethyl)carbazole was reportedly formed^{234a} (cf. ref. 230).

Methanol adds to NVC to give the ether 63 (R¹ = Me, R² = Me) in the presence of chloranil; this process is faster with light catalysis.^{235,236} A minor product in reaction at 65°C is a dimer (see p. 118).

²²⁷ A. Schouteeten and M. Julia, *Tetrahedron Lett.*, 607 (1975).

²²⁸ J. Pielichowski, *Rocz. Chem.* **40**, 1765 (1966).

²²⁹ T. Talik and J. Pielichowski, *Rocz. Chem.* **41**, 849 (1967) [*CA* **67**, 116783v (1967)].

²³⁰ J. Pielichowski and T. Talik, *Rocz. Chem.* **12**, 2161 (1969) [*CA* **72**, 111201x (1970)].

²³¹ J. Pielichowski and Z. Darzkiewicz, *Rocz. Chem.* **49**, 1581 (1975) [*CA* **84**, 43751x (1976)].

²³² H. H. Friederich and D. Lausberg, German Patent 1,005,964 (1957) [*CA* **53**, P18058h (1959)].

²³³ J. Pielichowski and T. Talik, *Rocz. Chem.* **42**, 591 (1968) [*CA* **71**, 38719v (1969)].

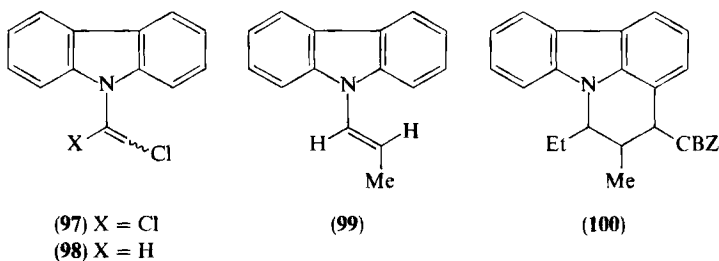
²³⁴ G. J. M. Van der Kerk and J. G. Noltes, *J. Appl. Chem.* **9**, 106 (1959).

^{234a} J. Breitenbach and J. Polaczek, *Monatsh. Chem.* **102**, 711 (1971).

²³⁵ L. P. Ellinger, *Polymer* **6**, 549 (1965).

²³⁶ L. P. Ellinger, *Polymer* **5**, 559 (1964).

9-Ethynylcarbazole was apparently formed by sodamide treatment of 9-dichlorovinylcarbazole (**97**) and zinc reduction of **97** gave **98**.²³⁷ Where no reaction occurred with the *Z* isomer, **99** gave the dimer **100** with boron trifluoride; the process presumably involves Lewis acid-catalyzed alkylation of one double bond by another double bond, complexed to boron trifluoride, followed by intramolecular Friedel-Crafts type alkylation at the carbazole 1-position.²³⁸



In a much studied transformation, 9-vinylcarbazole undergoes cyclodimerization, producing the head-to-head *trans*-cyclobutane dimer **92** under a variety of conditions. The dimer²³⁹ was obtained on irradiation in methanol solution in the presence of chloranil at 10°C.²³⁵ Iron(III) nitrate in methanol was also found to produce the dimer rapidly and in good yield.^{240,241} The presence of 2,2'-dipyridyl decreased the competing methanol addition to the vinyl group.²⁴² Pulse radiolysis in acetonitrile solution in the presence of oxygen,²⁴³ (see later) electrolysis,^{244,245} and singlet oxygen,²⁴⁶ best when generated by the decomposition of triphenylphosphite ozonide, have all been shown to bring about the formation of the same cyclodimer.

Both iron(III) and cerium(IV) salts in methanol transformed (*E*)-9-propenylcarbazole into a comparable dimer (**101**); however, the *Z* isomer, in which steric factors restrict conjugation between the double bond and the

²³⁷ Y. Okamoto and S. K. Kundu, *J. Org. Chem.* **35**, 4250 (1970).

²³⁸ S. G. Gorbachev, V. D. Filimonov, and E. E. Sirotkina, *Vysokomol. Soedin., Ser. B* **21**, 125 (1979) [*CA* **90**, 204558f (1979)].

²³⁹ L. P. Ellinger, J. Feeney, and A. Ledwith, *Monatsh. Chem.* **96**, 131 (1965).

²⁴⁰ C. E. H. Bawn, A. Ledwith, and Y. Shih-hin, *Chem. Ind. (London)*, 769 (1965).

²⁴¹ S. McKinley, J. V. Crawford, and C. H. Wang, *J. Org. Chem.* **31**, 1963 (1966).

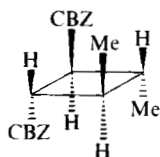
²⁴² F. A. Bell, R. A. Crellin, H. Fujii, and A. Ledwith, *Chem. Commun.*, 251 (1969).

²⁴³ S. Tagawa, S. Arai, M. Imamura, Y. Tabata, and K. Oshima, *Macromolecules* **7**, 262 (1974).

²⁴⁴ J. W. Breitenbach, O. F. Olaj, and F. Wehrmann, *Monatsh. Chem.* **95**, 1007 (1964).

²⁴⁵ D. H. Davies, D. C. Phillips, and J. D. B. Smith, *J. Org. Chem.* **38**, 2562 (1973).

²⁴⁶ S. Nishimoto and T. Kagiya, *Chem. Lett.*, 973 (1978).

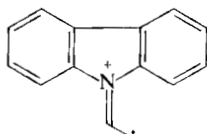


(101)

nitrogen, failed to dimerize.^{242,247} The rate of photochemical dimerization of the (*E*)-9-propenylcarbazole was one-tenth that of 9-vinylcarbazole.²⁴⁷

Most mechanistic work²⁴⁷⁻²⁵⁴ on *N*-vinylcarbazole dimerization has been carried out on the photocatalyzed process conducted in the presence of a sensitizer and oxygen or another oxidant, such as Cu(II) heptanoate.²⁴⁷ Several workers have noted that in the absence of oxygen, polymer instead of cyclodimer is produced.^{247,252,253} Chloranil,²⁴⁹ fluorenone,²⁴⁹ rhodamine 6G,²⁴⁷ and phthalic anhydride²⁵¹ are among the photosensitizers²⁵¹ that have been used.

The various methods that convert *N*-vinylcarbazole to the cyclodimer all depend on the generation of a radical cation; one resonance contributor (102) to which shows the radical character essential to explain the head-to-head linking and the role of nitrogen in stabilizing the cationic center. This much-studied dimerization process, including a consideration of the role of oxygen, has been discussed elsewhere.^{240,241,245,246,248-251,254}



(102)

Cycloaddition of 9-vinylcarbazole to tetracyanoethylene took place in benzene solution giving **103**, but in methanol the diene **104** was obtained; cyclobutane (**103**) itself was transformed into **104** in methanol.²⁵⁵ Other

²⁴⁷ R. A. Crellin and A. Ledwith, *Macromolecules* **8**, 93 (1975).

²⁴⁸ R. A. Carruthers, R. A. Crellin, and A. Ledwith, *Chem. Commun.*, 252 (1969).

²⁴⁹ R. A. Crellin, M. C. Lambert, and A. Ledwith, *Chem. Commun.*, 682 (1970).

²⁵⁰ K. Hamanoue, H. Teranishi, M. Okamoto, Y. Tarukawa, S. Tagawa, and T. Yoncho, *J. Polym. Sci., Polym. Chem. Educ.* **18**, 91 (1980).

²⁵¹ K. Tada, Y. Shirota, S. Kusabayashi, and H. Mikawa, *Chem. Commun.*, 1169 (1971).

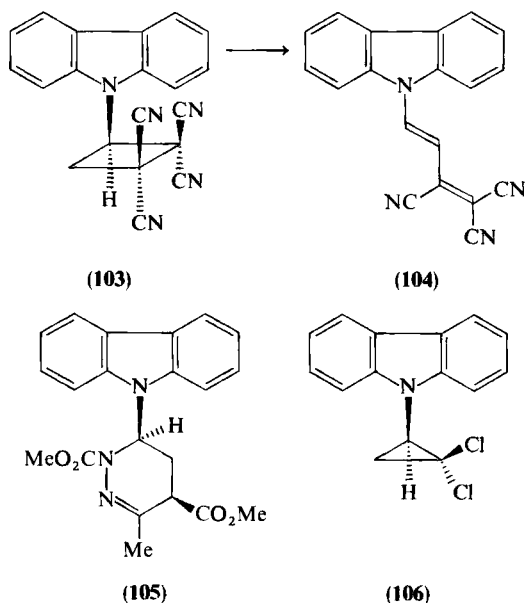
²⁵² Y. Shirota, K. Tada, M. Shimizu, S. Kusabayashi, and H. Mikawa, *Chem. Commun.*, 1110 (1970).

²⁵³ C.-H. Wang, C. C. Sizman, and K. Stevenson, *J. Org. Chem.* **35**, 2045 (1970).

²⁵⁴ S. Tazuke and N. Kitamura, *J. C. S. Chem. Commun.*, 515 (1977).

²⁵⁵ C. E. H. Bawn and A. Ledwith, *Polymer* **12**, 209 (1971).

cycloadditions involving the double bond of 9-vinylcarbazole are its reaction with the diazadiene $\text{MeO}_2\text{C}-\text{N}=\text{N}-\text{C}(\text{Me})=\text{CHCO}_2\text{Me}$ forming the tetrahydropyridazine **105**²⁵⁶ and the formation of the dichlorocyclopropane **106** with dichlorocarbene.²⁵⁷



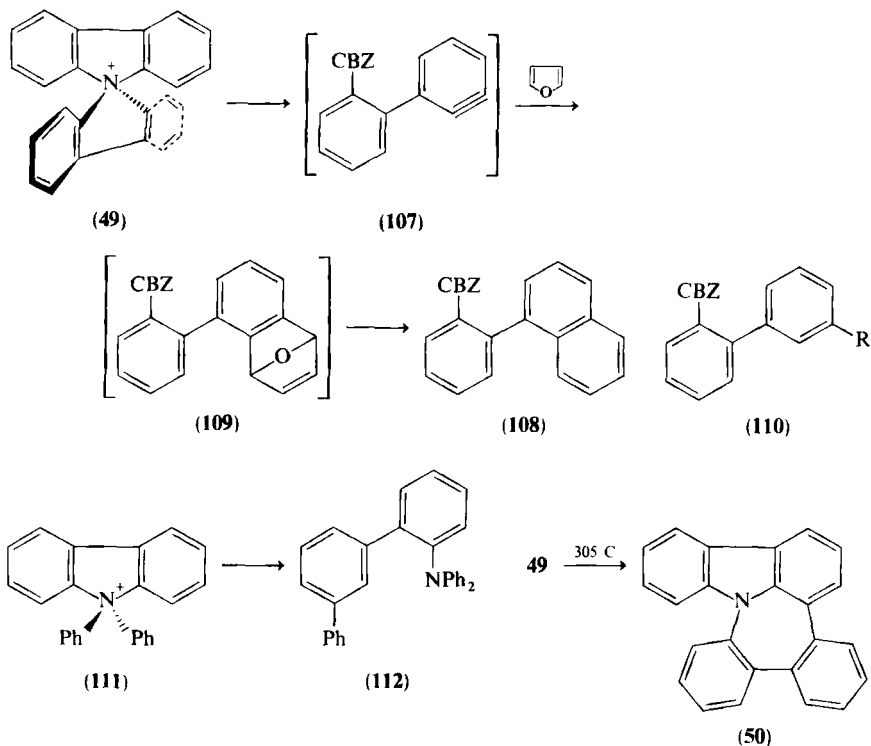
3. Aryl

Phenyl,^{134,211} 2-phenylphenyl,¹³⁴ and 2-(3-phenylphenyl)phenyl¹³⁴ groups can be cleaved from carbazole nitrogen with lithium.

Strong base treatment of the spiro salt **49** gives a benzyne (**107**) from which the isolated products were produced by further reaction. For example, with *n*-butyllithium and furan in tetrahydrofuran, **108** is produced after hydrogenation and acid treatment via **109**. Reaction with phenyllithium gives **110** (R = Ph and Me) by subsequent addition of phenyl or methyl anion to the benzyne, respectively, and **110** (R = I) by subsequent reaction with iodine anion. Similarly the 9,9-diphenyl salt **111** gives **112** with phenyllithium. Pyrolysis of the spiro salt **49** gives **50**.¹³⁴

²⁵⁶ S. Sommer, *Chem. Lett.*, 583 (1977).

²⁵⁷ M. Makosza and A. Kacprowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **22**, 467 (1974) [*CA* **81**, 151900s (1974)].



4. Acyl

Acyl groups are easily hydrolytically removed from carbazole nitrogen, done best with alkali,⁶¹⁻⁶⁶ or by exposure to alumina²⁵⁸ or under more vigorous conditions with aqueous acid.²⁵⁹

Lithium aluminium hydride treatment of 9-acylcarbazoles also regenerates the carbazole.²⁶⁰ At low temperature, reduction of the acyl residue proceeds only as far as the aldehyde oxidation level, and this provides a means for the conversion of acid to aldehyde via the 9-acylcarbazole. This process has been described for the preparation of benzaldehyde,²⁶¹ cinnamaldehyde,¹⁴⁸ and various α -amino aldehydes.¹⁵³ Reduction of 9-ethoxycarbonylcarbazole gave 9-hydroxymethylcarbazole.²⁶² Mechanistically

²⁵⁸ E. Funakubo, Y. Matsumoto, and G. Kon, *Z. Phys. Chem.* **223**, 161 (1963).

²⁵⁹ P. Hyde, L. J. Kricka, and A. Ledwith, *Polymer* **14**, 124 (1973).

²⁶⁰ K. Barholzer, T. W. Campbell, and H. Schmid, *Helv. Chim. Acta* **35**, 1577 (1952).

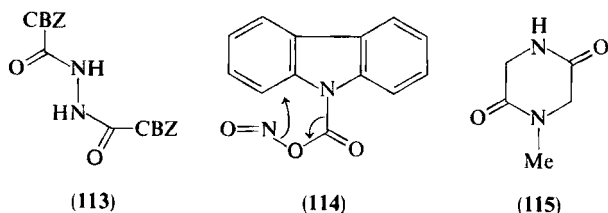
²⁶¹ V. M. Mićović and M. Lj. Mihailović, *J. Org. Chem.* **18**, 1190 (1953).

²⁶² J. Knabe, *Arch. Pharm (Weinheim, Ger.)* **288**, 469 (1955).

comparable to these hydride addition processes is the reaction of the phenyl Grignard reagent with 9-benzoylcarbazole, which gave carbazole and trityl alcohol.²⁶³

9-Acetylcarbazole was reportedly converted to the dichlorovinyl derivative **97** using phosphorus pentachloride in refluxing benzene.²³⁷

9-Chloroformylcarbazole reacts with 2-alkylaminoethanols and -ethanamines to give the corresponding urethanes and ureas,¹⁶³ with hydrazine to give **113**,²⁶⁴ and with nitrous acid to give 9-nitrosocarbazole in good yield. The four-membered cyclic transition state **114** is envisaged to rationalize the latter reaction.²⁶⁵ The halogen of 9-chloroacetylcarbazole was displaced conventionally by nitrogen of diethylamine¹⁵⁹ and that of 9-(3-bromopropionyl)carbazole by the diketopiperazine **115**.¹⁶² Sodium iodide and sodium acetate bring about elimination of hydrogen chloride from 9-(3-chloropropionyl)carbazole producing 9-acrylylcarbazole.¹⁶¹



Pyrolysis of 9-methoxycarbonylcarbazole gives 9-methylcarbazole and carbon dioxide, whereas similar treatment of 9-ethoxycarbonylcarbazole led to ethene, carbon dioxide, and carbazole¹⁵⁰; the latter was shown to proceed with first-order kinetics.²⁶⁶

Fries rearrangement of 9-acetylcarbazole gives 3-acetylcarbazole^{267,268}; the reaction is best carried out in the presence of acetyl chloride.²⁶⁸ 3-Phenacetylcarbazole was likewise prepared from 9-phenacetylcarbazole.¹¹⁸ Photo-Fries rearrangement of *N*-acetylcarbazole in cyclohexane gave 1- and 3-acetylcarbazoles in roughly equal proportions²⁶⁹ and was used for the synthesis of the 1-isomer by Photo-Fries rearrangement in isopropanol.²⁷⁰

²⁶³ A. Mustafa, W. Asker, O. H. Hishmat, A. F. A. Shalaby, and M. Kamel, *J. Am. Chem. Soc.* **76**, 5447 (1954).

²⁶⁴ W. Ried, H. Hillenbrand, and G. Oertel, *Justus Liebigs Ann. Chem.* **590**, 123 (1954).

²⁶⁵ M. Nakajima and J. P. Anselme, *Tetrahedron Lett.*, 3831 (1979).

²⁶⁶ E. Dyer and G. C. Wright, *J. Am. Chem. Soc.* **81**, 2138 (1959).

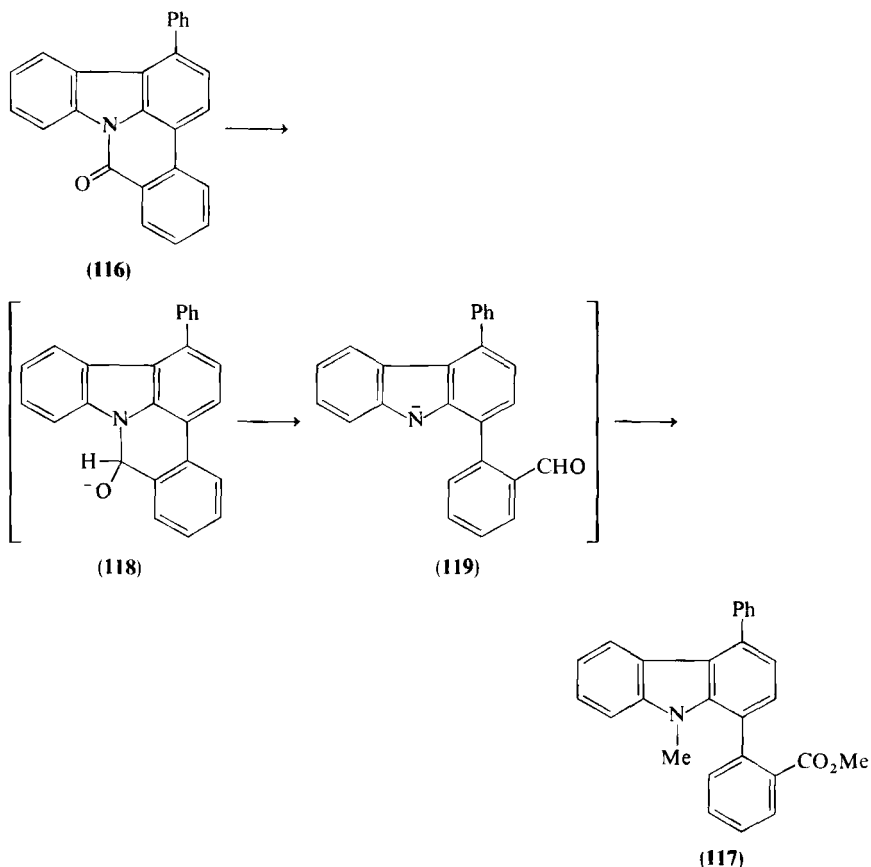
²⁶⁷ Yu. G. Yur'ev, V. P. Lopatinskii, V. L. Ivashenko, I. S. Isaev, and M. I. Gorfinkel, *Zh. Org. Khim.* **8**, 1755 (1972) [*CA* **77**, 139705s (1972)].

²⁶⁸ Yu. G. Yur'ev, V. L. Ivashenko, and V. P. Lopatinskii, *Izv. Tomsk. Politekh. Inst.* **257**, 66 (1973) [*CA* **82**, 16653n (1975)].

²⁶⁹ H. Shizuka, M. Kato, T. Ochiai, K. Matsui, and T. Morita, *Bull. Chem. Soc. Jpn.* **43**, 67 (1970).

²⁷⁰ G. N. Ivanov, V. Ya. Tolmacheva, and V. P. Lopatinskii, *Izv. Tomsk. Politekh. Inst.* **250**, 162 (1975) [*CA* **86**, 106287q (1977)].

The strange conversion of **116** into **117** with sodium hydride in dimethylformamide followed by methyl iodide was explained as involving sodium hydride as a hydride donor, thence the intermediates **118** and **119**.²⁷¹

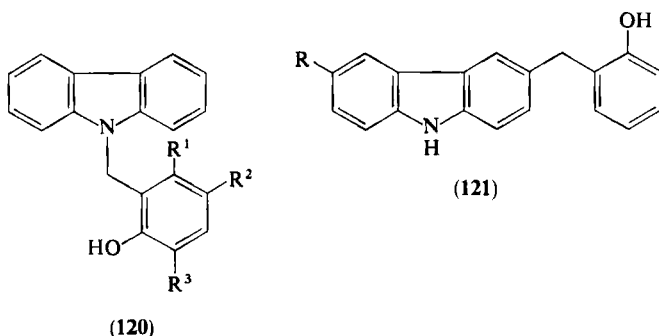


5. Oxy- and Aminoalkyl

9-Hydroxymethylcarbazole can be O-benzoylated in pyridine with benzoyl chloride.²¹⁴ Using concentrated hydrochloric acid at 20°C or polyphosphoric acid at 100°C, it was converted to the ether **64** (R = H).²⁷¹ It reacts with phenol, or with phenols carrying additional alkyl or hydroxyl

²⁷¹ V. F. Traven, V. A. Smrcek, and B. I. Stepanov, *Khim. Geterotsikl. Soedin.*, 568 (1967) [*CA* **68**, 39407s (1968)].

groups, to give substitution products **120** ($R^1 = R^2 = R^3 = H$; $R^1 = R^2 = H$, $R^1 = Me$; $R^1 = R^3 = H$, $R^2 = Me$; $R^1 = R^2 = Me$, $R^3 = H$; $R^1 = OH$, $R^2 = R^3 = H$).²⁷² 9-Benzoyloxymethylcarbazole and its 3-chloro, 3,6-dichloro, and 3-nitro analogs gave comparable products (**120**) but only under acid catalysis. However, the use of acid with 9-hydroxymethylcarbazoles led to 3-substitution and the formation of **121** ($R = H$, Cl , and NO_2).²⁷² 9,9'-Dicarbazolylmethane is formed from 9-hydroxymethylcarbazole on treatment with acetic acid or from its acetate on reaction with carbazol-9-ylmagnesium iodide.¹⁸⁶



The acetoxy group of 9-(1-acetoxyethyl)carbazole is easily displaced with alcohols.^{154,182} Easy displacement of a similarly situated halogen can be achieved, as has been noted before (see Section II,C,2); thus methanol converts 9-(1-chloro-2-iodoethyl)carbazole to 9-(2-iodo-1-methoxyethyl)carbazole.²³¹ Elimination of acetic acid¹⁸² or ethanol²⁷³ by strongly heating 9-(1-acetoxyalkyl)- or 9-(1-ethoxyalkyl)carbazoles gives 9-vinylcarbazoles. In the absence of acid, (*E*)-alkenes are produced, but acid catalysis leads to a mixture of *E* and *Z* isomers.²⁷³ Acetyl chloride in pyridine also effects ethanol elimination.²⁷⁴

Methanolysis of 9-(1-methoxyethyl)carbazole with methanol-hydrogen chloride gave carbazole and acetaldehyde dimethyl acetal.²³⁶ 9,9'-Di-(3,6-dibromocarbazolyl)methane gave 9-acetyl-3,6-dibromocarbazole with acetic anhydride and a trace of sulfuric acid.¹⁸⁷

²⁷² V. Ya. Tolmacheva, I. P. Zhrebtssov, V. P. Lopatinskii, and N. I. Shardakova, *Zh. Org. Khim.* **18**, 157 (1982) [*CA* **96**, 142628s (1982)].

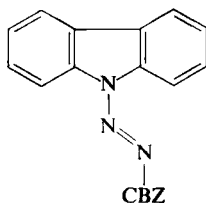
²⁷³ V. D. Filimonov, V. A. Anfinogenov, and E. E. Sirotkina, *Khim. Geterotsikl Soedin.*, 497 (1979) [*CA* **91**, 74404k (1979)].

²⁷⁴ V. D. Filimonov, V. A. Anfinogenov, and E. E. Sirotkina, *Zh. Org. Khim.* **14**, 2607 (1978) [*CA* **90**, 103763p (1979)].

6. Nitrogen

9-Nitrosocarbazoles can be reduced to 9-aminocarbazoles with lithium aluminium hydride^{55,194} or zinc-acetic acid,²⁷⁵⁻²⁷⁷ the latter being useful for carbazoles that also carry C halogen.²⁷⁷ The 9-nitroso group can be hydrolytically removed with alkali.¹⁹³ The 9-nitroso group has been oxidized to a nitro group using *meta*-chloroperbenzoic acid, although 1-nitrocarbazole and some 3-nitrocarbazole were also produced. Heating 9-nitrosocarbazole in xylene or 9-nitrocarbazole in benzene in each case produced a mixture of 1- and 3-nitrocarbazoles.²⁷⁸

9-Nitrosocarbazole condenses with 9-aminocarbazole to give the azo compound **122**, heating of which produces dimers in a ratio similar to that observed by oxidation of carbazole (see Section II.A,2); it was therefore believed to involve the carbazol-9-yl radical.²⁵ 3-Nitro-9-nitrosocarbazole was shown to serve as a nitrosating agent for *N*-methylaniline; it converted aziridine to ethene and nitrous oxide.²⁷⁹



(122)

9-Aminocarbazole behaves as an arylhydrazine in reactions with aldehydes^{194,277} and ketones,¹⁹⁴ with the imine condensation products being reducible with sodium borohydride or lithium aluminium hydride.¹⁹⁴ In reacting as an aromatic amine, 9-aminocarbazole formed a benzamide,²⁷⁶ a formamide with dimethyl formamide-benzenesulfonyl chloride, a benzenesulfonamide with pyridine-benzenesulfonyl chloride, and even a dibenzenesulfonamide with triethylamine-benzenesulfonyl chloride—dimethylformamide, the latter being convertible to the monobenzenesulfonamide with sodium methoxide. Surprisingly, some *N*-methylated derivative was also formed in

²⁷⁵ D. M. Lemal, T. W. Rave, and S. D. McGregor, *J. Am. Chem. Soc.* **85**, 1944 (1963).

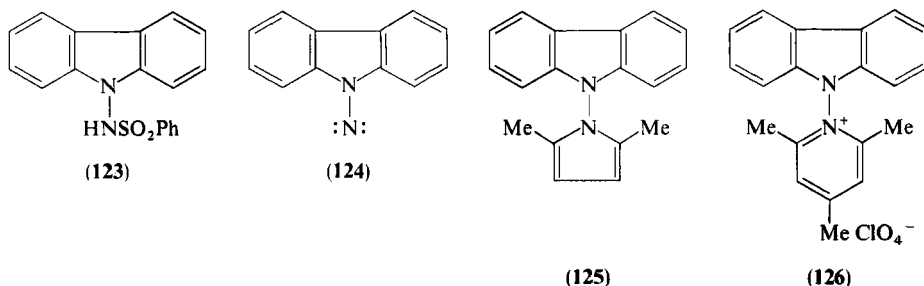
²⁷⁶ P. A. S. Smith and H. G. Pars, *J. Org. Chem.* **24**, 1325 (1959).

²⁷⁷ R. O. Matevosyan, I. Ya. Postovskii, and A. K. Chirkov, *Zh. Obshch. Khim.* **30**, 3186 (1960) [*CA* **55**, 18704g (1961)].

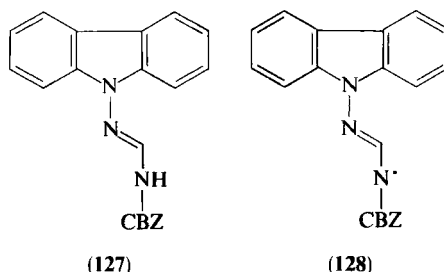
²⁷⁸ P. Welzel, *Chem. Ber.* **104**, 808 (1971).

²⁷⁹ C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.* **83**, 4417 (1961).

this last reaction.²⁷⁵ Vigorous treatment of **123** with sodium methoxide–tetraglyme at 275°C gave carbazole, a process believed to proceed via the nitrene **124** and the diazazene **122**.²⁷⁵ Diazotization with isoamyl nitrite in tetrafluoroboric or acetic acids converted it to carbazole.²⁸⁰ The 9-amino group acted normally in reaction with a 1,4-diketone forming pyrrole **125**²⁸¹ and with an unsaturated 1,5-dicarbonyl equivalent, 2,4,6-trimethylpyrylium perchlorate, in giving the pyridinium salt **126**.²⁸²



Condensation of 2-mol equivalents of 9-aminocarbazole with ethyl orthoformate–boron trifluoride yielded the formamidine **127**, which was oxidized with lead dioxide to the spectrally observable radical **128** in solution.^{55,283}



Triethyltin hydride promotes the radical decomposition of **128** giving carbazole.²⁸⁴ The dimer **129** (R = H) decomposed in dry benzene at room temperature giving carbazole (10%) and 9-anilino-carbazole (20%) and other unidentified products.²⁸⁵ However **129** (R = Me) gave **130**, which on warm-

²⁸⁰ M. De Rosa and P. Haberfield, *J. Org. Chem.* **46**, 2639 (1981).

²⁸¹ H. S. Broadbent, W. S. Burnham, P. K. Olsen, and R. M. Sheeley, *J. Heterocycl. Chem.* **5**, 757 (1968).

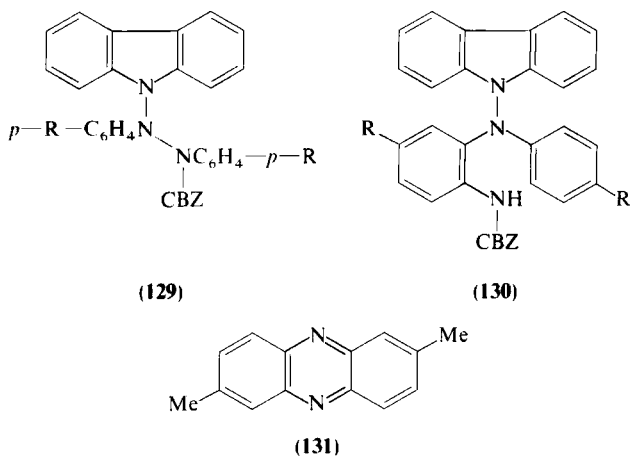
²⁸² A. R. Katritzky and J. W. Suwinski, *Tetrahedron Lett.*, 4123 (1974).

²⁸³ F. A. Neugebauer and H. Trischmann, *Monatsh. Chem.* **97**, 554 (1966).

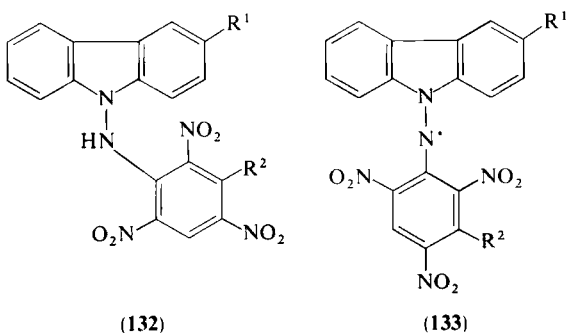
²⁸⁴ J. Hollaender, W. P. Neumann, and H. Lind, *Chem. Ber.* **106**, 2395 (1973).

²⁸⁵ L. Benati, G. Placucci, P. Spagnolo, A. Tundo, and G. Zanardi, *J. C. S. Perkin I*, 1684 (1977); R. Benati, P. Spagnolo, A. Tundo, and G. Zanardi, *ibid.*, 1536 (1979).

ing in benzene cleanly gave 2-mol equivalents of carbazole and the phenazine **131**.



9-Aminocarbazole will displace halogen from activated benzenoid aromatics, thus compounds **132** ($R^1 = R^2 = H$; $R^1 = H, R^2 = Cl$; $R^1 = H, R^2 = N [CH_2]_2O$) were prepared.^{277,286-288} Such compounds can be oxidized with lead dioxide to *N*-picryl-9-aminocarbazyls (**133**). These black species are dehydrogenating agents; though stable in dry chloroform the transformation of violet-black color into orange in benzene solution suggests that they

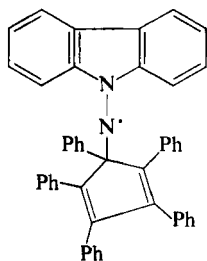


²⁸⁶ R. O. Matevosyan and L. I. Stashkov, *Zh. Org. Khim.* **1**, 2087 (1965). [*CA* **64**, 11152c (1966)]; I. B. Donskikh and R. O. Matevosyan, *Arm. Khim. Zh.* **31**, 368 (1978) [*CA* **89**, 129150r (1978)].

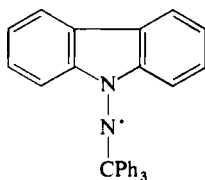
²⁸⁷ H. Makino, H. Nishiguchi, Y. Deguchi, and H. Takaki, *Tetrahedron Lett.*, 2267 (1968).

²⁸⁸ I. B. Donskikh and V. V. Sidorov, *Tr. Inst. Khim., Ural. Nauchn. Tsentr, Akad. Nauk SSSR* **34**, 58 (1975) [*CA* **87**, 39391z (1971)].

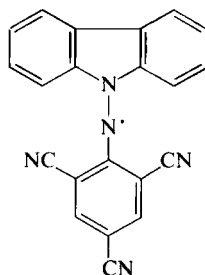
were "dehydrogenating" benzene.²⁸⁹ Hydrazyls **134**, **135**, and **136** were produced in solution by lead dioxide oxidation after preparation of the hydrazine from 9-aminocarbazole. These were the first hydrazyls produced that did not derive their stabilization by conjugation with aromatic nitro-groups.²⁹⁰



(134)

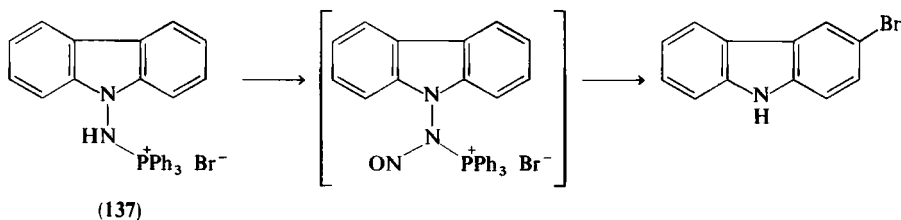


(135)



(136)

A mechanistically intriguing transformation resulted when 9-aminocarbazole formed salt **137** via the reaction of its Grignard derivative with dibromotriphenylphosphorane. Reaction of the salt **137** with ethyl nitrite gave 3-bromocarbazole; the authors speculate that nitrosation followed by nitrogen loss generates the carbazol-9-yl cation, attacked in a nucleophilic sense by bromide at C-3.²⁹¹



7. Sulfur

9-Tosylcarbazole is efficiently converted to carbazole with sodium isoamyloxide in isoamyl alcohol.²⁹² Phenylmagnesium bromide also brings about this change, phenyl *p*-tolyl sulfone being isolated as a cleavage prod-

²⁸⁹ R. O. Matevosyan, E. G. Gabriel'yan, A. K. Chirkov, and I. Ya. Postovskii, *Dokl. Akad. Nauk SSSR* **137**, 99 (1961) [*CA* **55**, 23491c (1961)].

²⁹⁰ D. Braun and G. Peschk, *Angew. Chem., Int. Ed. Engl.* **7**, 945 (1968).

²⁹¹ E. Keschmann and E. Zbiral, *Justus Liebigs Ann. Chem.*, 1445 (1973).

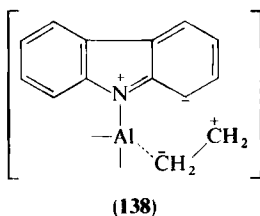
²⁹² D. Klamann and H. Bertsch, *Chem. Ber.* **91**, 1427 (1958).

uct.²⁶³ The carbazole anion was generated in a fluorescent excited state by electrolytic cleavage of 9-tosylcarbazole or by treatment with butyllithium.²⁹³

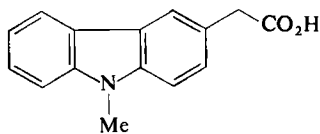
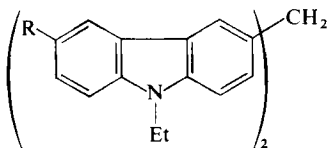
D. INTRODUCTION OF SUBSTITUENTS ONTO CARBAZOLE CARBON

1. Alkyl

Carbazole reacts with cyclohexene in a reaction catalyzed by aluminium chloride to give a low yield of 3-cyclohexylcarbazole and a main product of the 3,6-disubstituted material.²⁹⁴ The formation of 1-ethylcarbazole in high yield by treatment of carbazole and ethene at 300°C with aluminium-mercuric chloride and aniline is believed to proceed via **138**. 1-Isopropylcarbazole was similarly prepared using propene.²⁹⁵



The benzylic alcohol 6-bromo-9-ethylcarbazole-3-ylcarbinol alkylated 3-bromo-9-ethylcarbazole at the 6-position generating **139** (R = Br). Dicarbazol-3-ylmethanes also resulted from direct treatment of the 3-halo-9-ethylcarbazoles with formaldehyde-acetic acid and sulfuric acid, presumably via the 3-carbinols.^{296,297} High yield 3-monoalkylation of 9-methylcarbazole was



²⁹³ A. J. Bard, K. Itaya, R. E. Malpas, and Teherani, *J. Phys. Chem.* **84**, 1262 (1980).

²⁹⁴ Ng. Ph. Buu-Hoi, L. C. Binh, T. B. Loc, Ng. D. Xuong, and P. Jacquignon, *J. Chem. Soc.*, 3126 (1957).

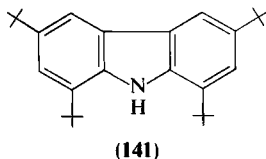
²⁹⁵ R. Strohm and W. Hahn, *Justus Liebigs Ann Chem.* **623**, 176 (1959).

²⁹⁶ P. Bruck, A. Ledwith, and A. C. Bell, *J. Chem. Soc. B*, 205 (1970).

²⁹⁷ K. Nishide, T. Yamanouchi, and K. Kingo, U.S. Patent 3,832,172 [CA **83**, P116993u (1975)].

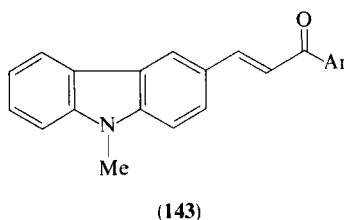
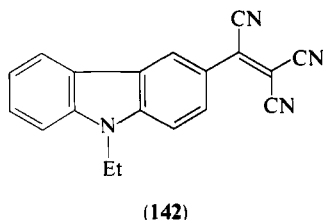
achieved with chloroacetic acid in potassium bromide-iron at 175°C giving **140**.²⁹⁸

Carbazole can be efficiently tetra-*tert*-butylated with *tert*-butylchloride and aluminium chloride at room temperature giving **141**^{40,41,85}; traces of 3,6-di- and 1,3,6-tri-*tert*-butylcarbazoles are also produced. 3-Formyl-2-hydroxycarbazole is alkylated at C-1 with dimethylallyl chloride in the presence of 30% aqueous potassium hydroxide.²⁹⁹



2. Alkenyl, Aryl, and Heteroaryl

9-Ethylcarbazole reacted at C-3 with tetracyanoethene in hot dimethylformamide generating **142**.³⁰⁰ A series of aryl chlorovinyl ketones reacted with 9-methylcarbazole at the 3-position to give monosubstitution products **143** utilizing aluminium chloride catalysis.³⁰¹



In the course of carbazole alkaloid syntheses, various phenolic carbazoles have been reacted with aldehydes. In at least some of these examples in which the isolation of a product identical with the target alkaloid was reported, it is likely that the isolated product was simply one of the isomeric products produced.

Citral reacted in pyridine with 2-hydroxy-3-methylcarbazole³⁰² and with 2-hydroxy-7-methoxy-3-methylcarbazole³⁰³ to give ethers **144** (R = H and

²⁹⁸ M. M. Sukhoroslova, V. P. Lopatinskii, and V. I. Sushkov, *Izv. Tomsk. Politech. Inst.* **268**, 67 (1976) [*CA* **87**, 134916h (1977)].

²⁹⁹ B. S. Joshi and D. F. Rane, *Chem. Ind. (London)*, 685 (1968).

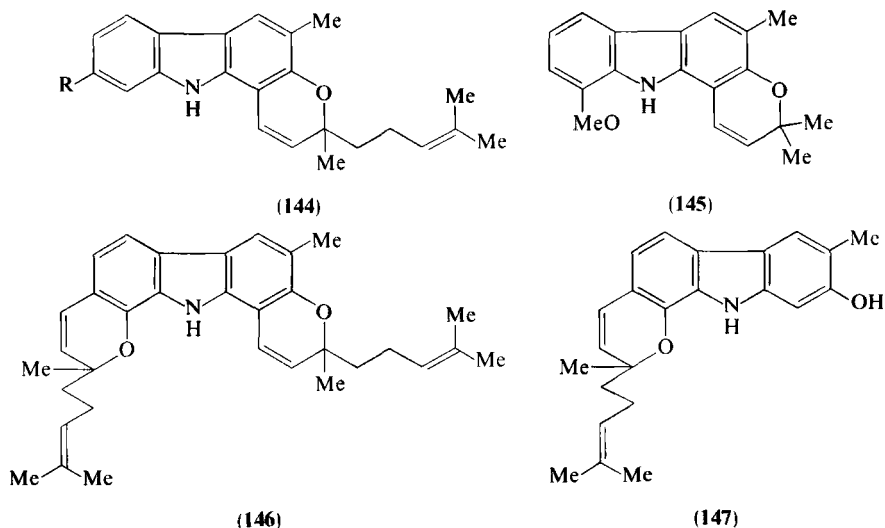
³⁰⁰ J. E. Kuder, W. W. Limburg, J. M. Pochan, and D. Wychick, *J. C. S. Perkin II*, 1643 (1977).

³⁰¹ V. F. Belyaev and A. I. Abrazhevich, *Khim. Geterotsikl. Soedin.*, 1359 (1973) [*CA* **80**, 47767x (1974)].

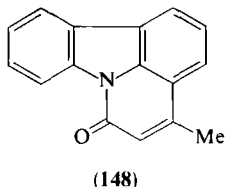
³⁰² S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. Commun.*, 1120 (1969).

³⁰³ F. Anwer, R. S. Kapil, and S. P. Popli, *Experientia* **28**, 769 (1972).

OMe). Reaction with 2-hydroxycarbazole itself gave a mixture of comparable ethers from condensation mainly at C-1 and some at C-3.³⁰⁴ The use of 3-hydroxy-isovaleraldehyde dimethyl acetal comparably led to **145** using 2-hydroxy-8-methoxy-3-methylcarbazole.³⁰⁵ In examples having two phenolic activating groups on different rings, attack occurred at alternative positions. Thus, 2,6-dihydroxy-3-methylcarbazole gave isolated ethers by condensation with 3-hydroxy-isovaleraldehyde dimethyl acetal³⁰⁶ or citral³⁰³ resulting from C—C bonding at C-1, whereas 2,7-dihydroxy-3-methylcarbazole reacted with citral at C-8.³⁰³ 2,8-Dihydroxy-3-methylcarbazole reacted to give a mixture of the di and mono ethers **146** and **147**, the latter resulting from attack ortho to the 8-hydroxyl group.³⁰³



9-Acetoacetylcarbazole cyclized with concentrated sulfuric acid to give the 1-substituted enone **148**.¹⁶⁹



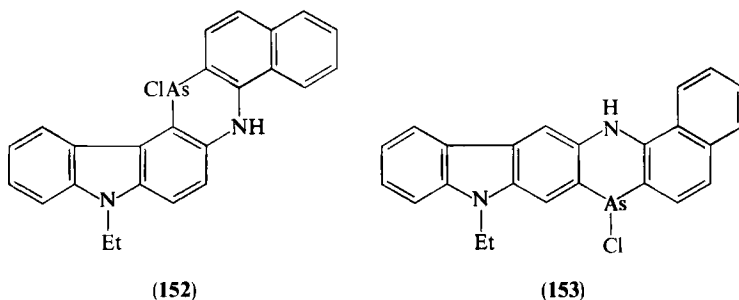
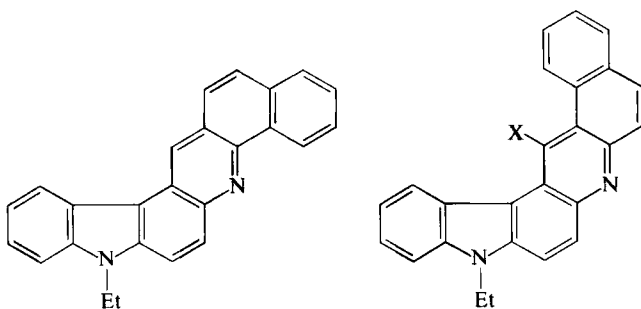
Various ring closures involving aminocarbazoles have been reported, but no clear pattern emerges from an examination of the direction of closure in

³⁰⁴ V. V. Kane, A. R. Martin, and J. A. Peters, *Heterocycles* **16**, 1445 (1981).

³⁰⁵ R. B. Sharma, R. Seth, F. Anwer, and R. S. Kapil, *Indian J. Chem., Sect. B* **20B**, 701 (1981).

³⁰⁶ S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. Ind. (London)* 1262 (1970).

which there are alternatives. 9-Ethyl-3-aminocarbazole reacted with formaldehyde and the two naphthols by C—C bonding at carbazole C-4 producing **149** from α -naphthol and its isomer **150** from β -naphthol.³⁰⁷ 9-Ethyl-3-naphthylaminocarbazole similarly condensed with acetic anhydride and zinc chloride yielding the angular isomer **151**. However, closure with arsenic trichloride led to an isomeric mixture of **152** and **153** types in both α - and β -naphthylamino series (illustrated for the α -isomer).³⁰⁷



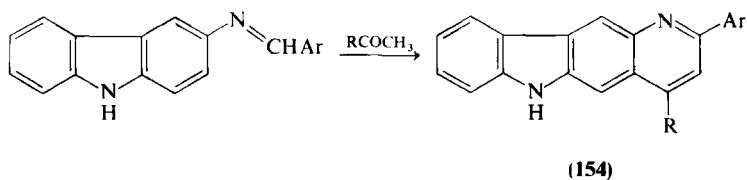
Schiff bases of 3-aminocarbazole were reported to react with ketones using mineral acid catalysis, through cyclization at C-2 giving **154**³⁰⁸ or at C-4 giving **155** (R = Me or Ar).³⁰⁹

The difference in direction of closure which was observed in the Skraup reaction of 9-ethyl-3-aminocarbazole that produced **156**²¹⁰ and in the

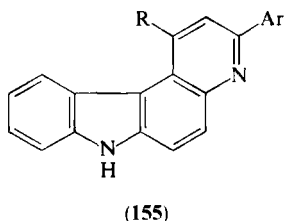
³⁰⁷ G. Saint-Ruf, J. C. Perche, and H. D. Phuoc, *Bull. Soc. Chim. Fr* 521 (1974).

³⁰⁸ V. V. Misenzhnikov and T. P. Shulyat'eva, *Khim. Khim. Tekhnol., Obl. Nauchno-Tekh. Konf. [Mater]*, 4th 1973, 2, 64 (1973) [*CA* **82**, 125299d (1975)]; N. S. Kozlov, V. V. Misenzhnikov, T. P. Shulyat'eva, and N. S. Vilisova, *Tezisy Dokl.-Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop.*, 2nd, 1973, 83 (1973) [*CA* **85**, 159943m (1976)].

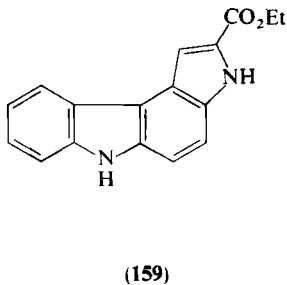
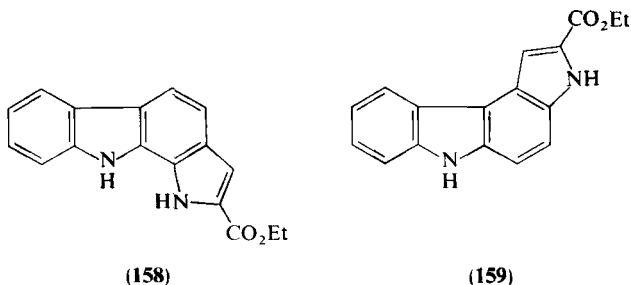
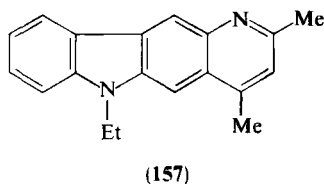
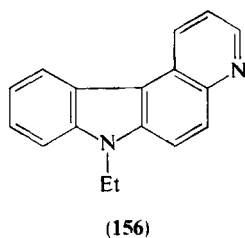
³⁰⁹ N. S. Kozlov, V. I. Letunov and N. N. Berdnik, *Dokl. Akad. Nauk. BSSR* **22**, 519 (1978) [*CA* **89**, 109173x (1978)]; V. I. Letunov, P. D. Rabinovich, and E. N. Tsvitsivadze, U.S.S.R. Patent 492,517 [*CA* **84**, P105561w (1976)].



or



Combes synthesis with pentan-2,4-dione that led to **157**, was ascribed to unfavorable steric hindrance in the alternative orientation in the Combes synthesis.²¹⁰ 2-Amino-1,4-dimethylcarbazole underwent the Skraup reaction in the only orientation available to it.³¹⁰ Finally, the carbazol-1-ylhydrazone of ethyl pyruvate underwent normal Fischer indolization giving **158**³¹¹; its 3-isomer gave an indole by cyclization at C-4 producing **159**.³¹²

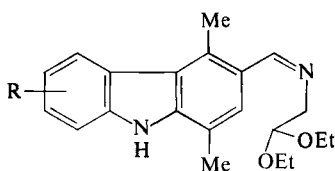


³¹⁰ J. Bergman and R. Carlsson, *Tetrahedron Lett.*, 4051 (1978).

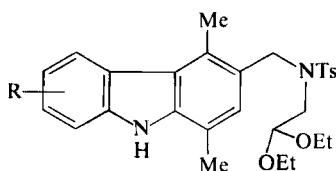
³¹¹ M. I. Sikharulidze, T. E. Khoshtariya, L. N. Kurkovskaya, L. G. Tret'yakova, T. K. Efimova, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1362 (1979) [*CA* **92**, 146649q (1980)].

³¹² T. E. Khoshtariya, M. I. Sikharulidze, L. G. Tret'yakova, T. K. Efimova, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 790 (1979) [*CA* **91**, 123652 (1979)].

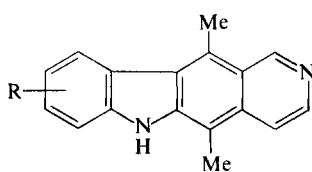
Following the pioneering examples,³¹³⁻³¹⁵ the acid catalyzed cyclization of systems **160**, or the dihydro-*N*-tosyl version **161**, has been much used³¹³⁻³²¹ for the formation of systems (**162**) of relevance to the alkaloid ellipticine **162** ($R = H$). The process has been achieved not only with the ellipticine system itself³¹³⁻³¹⁵ but also with 1,4,6- and 1,4,9-trimethylcarbazoles³¹⁵ and with 1,4-dimethyl-6,7-methylenedioxy carbazole,³¹⁶ 8-methoxy carbazole,³¹⁷ 6-bromocarbazole,³¹⁵ 6-methoxycarbazole,^{315,318} 6-methoxy-9-methylcarbazole,³¹⁵ 6-nitrocarbazole,^{315,319} 8-fluorocarbazole,³²⁰ 6,7-dimethoxycarbazole,³¹⁶ and 5,6,7-trimethoxycarbazole.³²¹ The only example in which a regio isomer has been reported is the case of the 3-formyl-1-methyl-6-methoxycarbazole-derived analog, which gave a small amount of the angular isomer **163** in addition to the linear pyridocarbazole.³¹⁸



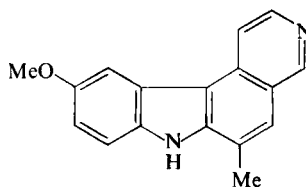
(160)



(161)



(162)



(163)

In the Elbs cyclization of the aryl ketone **164** ($R = \text{Me}$, $R^1 = H$) closure at both possible positions was observed forming **165** ($R = H$ and Me) and **166**

³¹³ P. A. Cranwell and J. E. Saxton, *Chem. Ind. (London)*, 45 (1962); *J. Chem. Soc.*, 3482 (1962).

³¹⁴ A. H. Jackson, R. R. Jenkins, and P. V. R. Shannon, *J. C. S. Perkin I*, 1698 (1977).

³¹⁵ L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Aust. J. Chem.* **20**, 2715 (1967).

³¹⁶ R. W. Guthrie, A. Brossi, F. A. Menziona, J. G. Mullin, R. W. Kierstead, and E. Grunberg, *J. Med. Chem.* **18**, 755 (1975).

³¹⁷ J. Y. Lallemand, P. Lemaitre, L. Beeley, P. Lesca, and D. Mansuy, *Tetrahedron Lett.*, 1261 (1978).

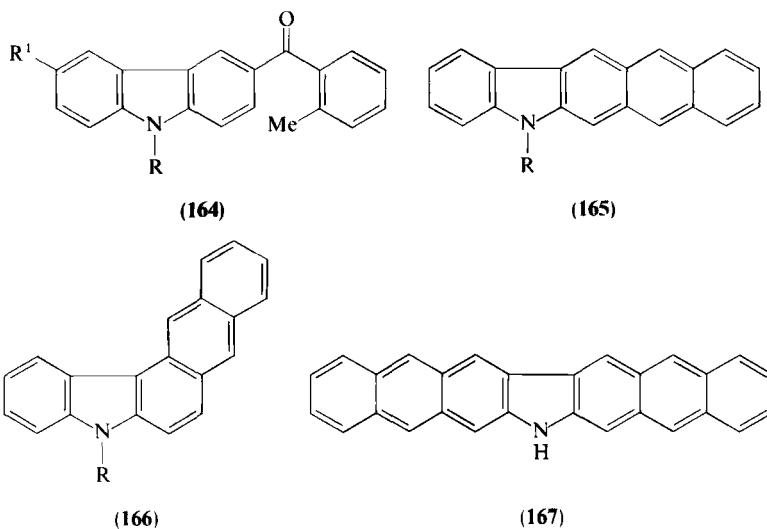
³¹⁸ J. Gilbert, D. Rouselle, C. Gansser, and C. Viel, *J. Heterocycl. Chem.* **16**, 7 (1979).

³¹⁹ C. Gansser, C. Viel, C. Malvy, and S. Cros, *Farmaco, Ed. Sci.* **35**, 887 (1980).

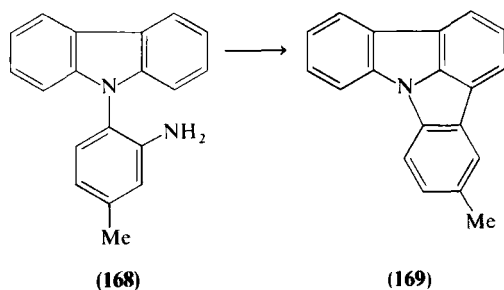
³²⁰ G. N. Taylor, *J. Chem. Res., Synop.*, 332 (1981).

³²¹ M. J. E. Hewlins, A. H. Jackson, A. M. Oliveira-Campos, and P. V. R. Shannon, *J. C. S. Perkin Trans. I*, 2906 (1981).

(R = H and Me). However, from the diketone **164** (R = H, R¹ = 2-methylbenzoyl) only the linear isomer **167** resulted.³²²



Intramolecular 1-arylation was achieved via the diazonium salt derived from **168** giving **169**.¹³⁵

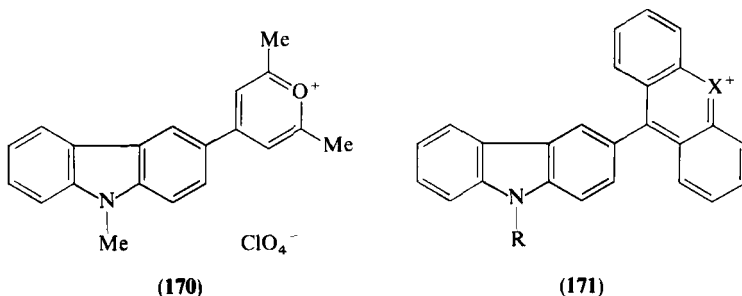


9-Methylcarbazole reacted with 2,6-dimethyl-4-pyrone in the presence of phosphorus oxychloride generating the pyrylium salt **170**.¹⁴⁴ Xanthydrol and thiaxanthydrol condensed with carbazole and 9-methylcarbazole under acid catalysis and sulfuric acid oxidation³²³ to give the colored salts **171** (X = O or S); the process has been used for the colorimetric determination of carbazole.^{323,324}

³²² M. Zander and W. Franke, *Chem. Ber.*, **96**, 699 (1963).

³²³ G. Gilbert, R. M. Stickel, and H. H. Morgan, *Anal. Chem.* **31**, 1981 (1959).

³²⁴ E. Sawicki and V. T. Oliverio, *J. Org. Chem.* **21**, 183 (1956).



3. Acyl

The propensity for 3-acylation of carbazole under Friedel-Crafts conditions and for further reaction to 3,6-diacylated carbazoles has long been known. 9-Alkylcarbazoles are somewhat less reactive. 9-Methyl-, 9-ethyl-, 9-*n*-propyl-, and 9-isopropylcarbazoles can be monoacetylated by adding the acid chloride last,³²⁵ although other workers reported diacetylation of 9-methyl-, 9-ethyl-, 9-isopropyl-, 9-*n*-butyl-, 9-*n*-amyl-, and 9-isoamylcarbazoles under very similar conditions.^{158,326,327} 9-Methylcarbazole gave 3-monoisobutyrylcarbazole by aluminium chloride-catalyzed reaction in benzene, but both 9-methylcarbazole and carbazole gave the diacyl derivatives in nitrobenzene solution at 0°C.³²⁷ 9-Isobutylcarbazole has been mono-3-acetylated with acetyl chloride-aluminium chloride.⁶³ 9-Isoamylcarbazole has been 3-mono-phenylacetylated, and 3-chloro-9-*n*-butylcarbazole has been converted to 3-acetyl-6-chloro-9-*n*-butylcarbazole.⁹⁴ Carbon disulfide as solvent gave a 35:15 mixture of di- and monoacetylcarbazoles with acid halide and aluminium halide,^{62,328} whereas in nitromethane a 77% yield of 3-acetylcarbazole was obtained.³²⁹ Zinc chloride in acetic acid at 150°C has been used to prepare 3-acetylcarbazole.³³⁰ 3,9-Diethylcarbazole gave the 6-acetyl derivative under the standard conditions, and although Vilsmeier formylation of 3,6,9-triethylcarbazole failed, acetylation with acetyl chloride and aluminium chloride produced the 1-acetyl substitution product.³³¹

³²⁵ V. P. Lopatinskii and E. E. Sirotkina, *Izv. Tomsk. Politekh. Inst.* **126**, 62 (1964) [*CA* **63**, 18007g (1965)].

³²⁶ V. P. Lopatinskii, E. E. Sirotkina, M. M. Anosova, and T. V. Sonina, *Izv. Tomsk. Politekh. Inst.* **136**, 18 (1965) [*CA* **65**, 16929h (1966)].

³²⁷ I. Kamiya and T. Sugimoto, *Bull. Chem. Soc. Jpn.* **54**, 25 (1981).

³²⁸ Y. Nagai and C.-C. Huang, *Bull. Chem. Soc. Jpn.* **38**, 951 (1965).

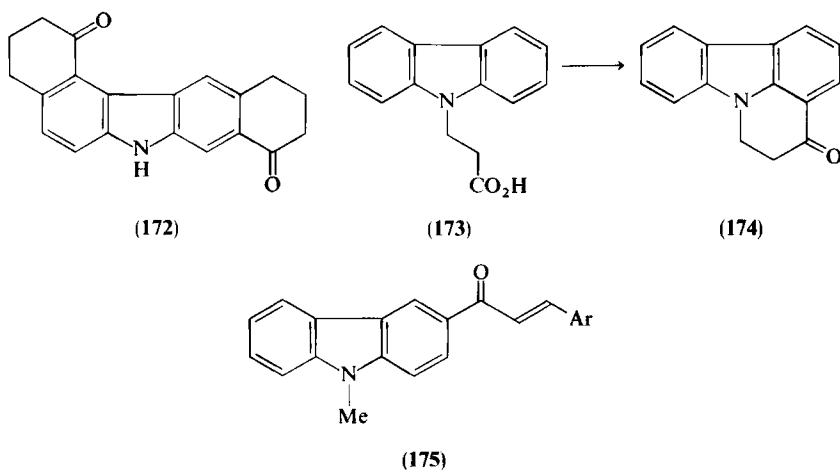
³²⁹ Yu. G. Yur'ev, V. L. Ivasenko, and V. P. Lopatinskii, *Izv. Tomsk. Politekh. Inst.* **257**, 50 (1973) [*CA* **82**, 161654v (1975)].

³³⁰ R. M. Acheson and B. F. Sansom, *J. Chem. Soc.*, 1900 (1953).

³³¹ Ng. Ph. Buu-Hoi, G. Saint-Ruf, and J. C. Perche, *Bull. Soc. Chim. Fr.*, 4126 (1967).

3-Acetylcarbazole has been prepared in yields up to 90% by the aluminium chloride catalyzed Fries rearrangement of 9-acetylcarbazole.^{267,268} Photo-Fries rearrangement of this substrate gave an equimolar mixture of 1- and 3-acetylcarbazoles in cyclohexane²⁶⁹; it has been used to prepare the 1-isomer by reaction in isopropanol.²⁷⁰ The Lewis acid-catalyzed Fries process was used to prepare 3-phenacetylcarbazole.¹¹⁹

Succinic anhydride gave the 3-monoacylated product³³² with 9-ethylcarbazole or the 3,6-diacylated product³³³ with carbazole itself. This last carbazole was reduced by the Clemmenson method and then intramolecularly cyclized with concentrated sulfuric acid, apparently regioselectively, to the diketone **172**.³³³ The 9-propanoic acid **173** was made to undergo intramolecular Friedel-Crafts acylation at the carbazole-1-position with hydrogen fluoride²²⁰ or trifluoroacetic anhydride³³⁴ producing **174**. *p*-Toluenesulfonyl isocyanate efficiently 3-sulfonamidoacylates carbazole³³⁵ β -Aryl- α,β -unsaturated acid chlorides acylate 9-methylcarbazole to give monosubstitution products **175** utilizing ferric chloride.³⁰¹



3-Benzoylcarbazole has been prepared in poor yield using anhydrous zinc chloride and benzoic acid at 160°C,³³⁰ using zinc chloride-benzoic anhydride at 150°C,³³⁶ and more efficiently by the Fries rearrangement of 9-benzoylcarbazole.³² A mixture of 3-mono- and 3,6-di-*o*-toluylcarbazoles resulted from the use of aluminium chloride in combination with acid chloride.³²²

³³² Ng, Ph. Buu-Hoi and D. Lavit, *Bull. Soc. Chim. Fr.*, 290 (1958).

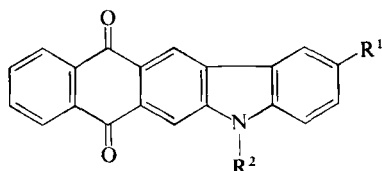
³³³ A. Rahman and O. L. Tombesi, *An. Asoc. Quim. Argent.* **62**, 109 (1974) [*CA* **81**, 135876h (1974)].

³³⁴ L. Toscano, E. Seghetti, and G. Fioriello, *J. Heterocycl. Chem.* **13**, 475 (1976).

³³⁵ M. Seefelder, *Chem. Ber.* **96**, 3243 (1963).

³³⁶ Ng, Ph. Buu-Hoi, R. Royer, and M. H. Habart, *J. Chem. Soc.*, 1082 (1955).

3-Amino-,^{337,338} 3-amino-9-methyl-, and 3-amino-9-(2-cyanoethyl)carbazoles and significantly 3-nitro-, 3-formyl-9-(2-cyanoethyl)-,^{338,339} and 3-formyl-9-alkylcarbazoles³³⁸ reportedly undergo a double acylation with phthalic anhydride giving the quinones **176**. Pyridine-2,3-dicarboxylic acid anhydride brought about the 3-monoarylation of 9-ethylcarbazole; attack at both of the pyridine carbonyl groups was observed.³⁴⁰



(176)

The tendency for 2-monoelectrophilic substitution of 9-acylcarbazoles has been used to make 2-acetyl-,^{61-63,259} 2-bromoacetyl-,⁶² 2-ethoxycarbonyl-,⁶² 2-propionyl-,⁶⁴ 2-ethoxycarbonylcarbonyl-,⁶⁵ and 2-(2-furoyl)carbazoles⁶⁶ with acetyl, bromoacetyl, and benzoyl as the group on nitrogen, by the subsequent hydrolytic removal of the 9-acyl group. Intramolecular 1-arylation was achieved using the acid **177**, obtained via lithiation and then carboxylation of 9-phenylcarbazole, with phosphorous pentachloride giving **178**.⁵¹

Vilsmeier formylation of carbazole can be conducted to give good yields of 3-monoformylcarbazoles³⁴¹: 9-methyl,^{342,343} 9-ethyl,^{344,345} 9-*n*-butyl, 9-isoamyl,³⁴³ and 9-isobutyl⁶³ derivatives were made in this way. The C-formylation of various carbazoles required for alkaloid and alkaloid analog synthesis makes instructive reading: 1,4-dimethyl-,^{313,315} 1,4,6-trimethyl-,^{313,315} 1,4,9-trimethyl-,³¹⁵ 1,4-dimethyl-6,7-methylenedioxy-,³¹⁶ 1,4-dimethyl-6,7-dimethoxy-,³¹⁶ 1,4-dimethyl-8-methoxy- (some N-formylation also obser-

³³⁷ L. A. Tsoi and Z. V. Pushkareva, *Zh. Prikl. Khim.* **36**, 1607 (1963) [*CA* **59**, 15409h (1963)].

³³⁸ V. I. Shishkina, L. A. Tsoi, M. K. Murshtein, and Z. V. Pushkareva, *Tr. Vses. Mezhvuz. Nauchno-Tekh. Konf. Vopr. Sint. Primen. Org. Krasitelei*, 1961, 17 (1962) [*CA* **60**, 14637b (1964)].

³³⁹ L. A. Tsoi, Z. V. Pushkareva, and V. F. Gryazev, *Zh. Obshch. Khim.* **34**, 284 (1964) [*CA* **60**, 10634f (1964)].

³⁴⁰ M. Ozutsuni, Y. Miyazawa, K. Motohasi, and T. Watanabe, *Ger. Offen.* 2,412,509 [*CA* **82**, P113184z (1975)].

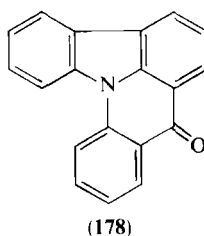
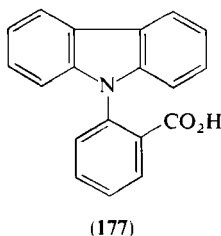
³⁴¹ M. Kuroki and Y. Tsunashima, *J. Heterocycl. Chem.* **18**, 709 (1981).

³⁴² V. M. Rodionov, F. Blanko, S. V. Bragin, A. M. Fedorova, A. B. Ershler, and A. I. Gryaznov, *Tr. Rostov. Khim.-Tekhnol. Inst. im. D. I. Mendeleeva* **23**, 13 (1956) [*CA* **52**, 20117f (1958)].

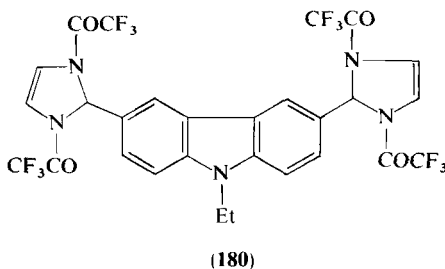
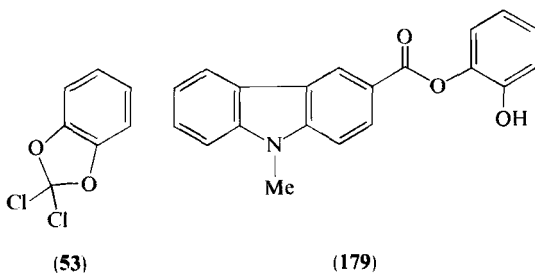
³⁴³ Ng. Ph. Buu-Hoi and Ng. Hoan, *J. Am. Chem. Soc.* **73**, 98 (1951).

³⁴⁴ E. E. Renfrew, U.S. Patent 3,948,938 [*CA* **85**, 7283h (1976)].

³⁴⁵ Ng. Ph. Buu-Hoi and Ng. Hoan, *J. Org. Chem.* **16**, 1327 (1951).



ved),³¹⁷ 1,4-dimethyl-6-methoxy-,^{315,318} 1,4,9-trimethyl-6-methoxy-,³¹⁵ 1,4-dimethyl-8-fluoro-,³²⁰ 1,4-dimethyl-6-nitro-,^{315,319} and 1,4-dimethyl-6-bromocarbazoles³¹⁵ all gave regioselective 3-formylation. In the case of 1,4-dimethyl-4,5,6-trimethoxycarbazole, 8-formylation (12%) and 3,8-diformylation (37%) occurred, although the main product was still the 3-formyl derivative (46%).³²¹ 6-Bromo-7-methoxy-1,4,9-trimethylcarbazole gave a complex mixture on exposure to the Vilsmeier reagent.³¹⁴ 2-Hydroxycarbazole formylated at 3- and 1-positions in a ratio of 3:1.^{299,346} 9-Ethylcarbazole reacted with imidazole-trifluoroacetic anhydride in high yield at both 3- and 6-positions to give **180** in which two carbon atoms at the oxidation level of aldehyde had been introduced.³⁴⁷



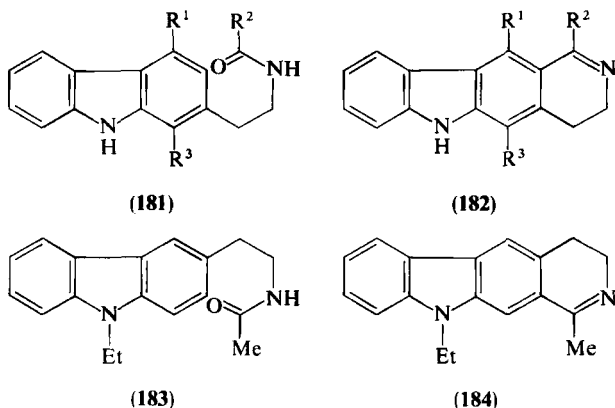
³⁴⁶ B. S. Joshi, V. N. Kamat, and D. F. Rane, *J. Chem. Soc. C*, 1518 (1969).

³⁴⁷ J. Bergman, L. Renström, and B. Sjöberg, *Tetrahedron* **36**, 2505 (1980).

Carboxylation of carbazol-9-ylpotassium gave a moderate yield of the 3-carboxylic acid.³⁴⁸ The Kolbe-Schmidt carboxylation of 2-hydroxycarbazole gave the 1-acid (50%) and the 3-acid as a minor product (12%).^{346,349} Lithiation³⁵⁰ of 9-methyl- or 9-ethylcarbazole and carboxylation gave the 1-carboxylic acids.⁵¹⁻⁵³

The dichloride **53** reacted with 9-methylcarbazole catalyzed by stannic chloride, leading to C-substitution at an unspecified position¹⁶⁴; presumably the product was **179**.

Phosphorus oxychloride or phosphorus pentoxide promoted Bischler-Napieralski cyclization of amides to the carbazole 3-position. This has been employed in alkaloid synthesis, thus **181** ($R^1 = H$, $R^2 = R^3 = Me$) gave **182** ($R^1 = H$, $R^2 = R^3 = Me$),³⁵¹⁻³⁵³ **181** ($R^1 = R^3 = Me$, $R^2 = H$) gave **182** ($R^1 = R^3 = Me$, $R^2 = H$),³⁵⁴ and **181** ($R^1 = Me$, $R^2 = H$, $R^3 = SMe$) gave **182** ($R^1 = Me$, $R^2 = H$, $R^3 = SMe$).³⁵⁵ With the side chain at C-3, cyclization apparently occurred only at C-2, **183** giving **184**.³⁵⁶



3-Amino-9-ethylcarbazole and its 6-methyl-homolog underwent the Conrad-Limpach reaction with ethyl acetoacetate, closure occurring at C-4 giving **185** ($R = H$ or Me).³⁵⁷ 1-Aminocarbazole condensed with diethyl ethoxymethylenemalonate to give **186**, which was thermally cyclized

³⁴⁸ Yu. L. Slominskii, *Tr. Stud. Nauchn. O-va., Khar'k. Politekh. Inst.* **5**, 155 (1962) [*CA* **61**, 4300g (1964)].

³⁴⁹ M. R. R. Bhagwath, A. V. R. Rao, and K. Venkataraman, *Indian J. Chem.* **7**, 1065 (1969).

³⁵⁰ R. H. Meen and H. Gilman, *J. Org. Chem.* **20**, 73 (1955).

³⁵¹ J. Schmutz and H. Wittwer, *Helv. Chim. Acta* **43**, 793 (1960).

³⁵² T. Naito, N. Iida, and I. Ninomiya, *J. C. S. Chem. Commun.*, 44 (1981).

³⁵³ E. Wenkert and K. G. Dave, *J. Am. Chem. Soc.* **84**, 94 (1962).

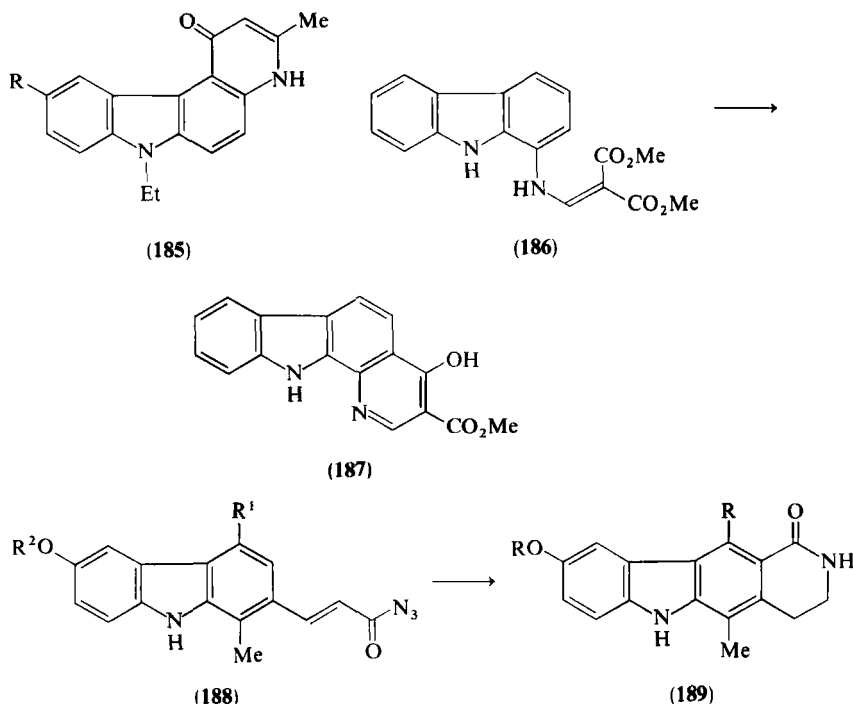
³⁵⁴ T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Indian J. Chem.* **1**, 247 (1963).

³⁵⁵ Y. Oikawa, M. Tanaka, H. Hirasawa, and O. Yonemitsu, *Chem. Pharm. Bull.* **29**, 1606 (1981).

³⁵⁶ M. J. Winchester and F. D. Popp, *J. Heterocycl. Chem.* **12**, 547 (1975).

³⁵⁷ J. C. Perche and G. Saint-Ruf, *J. Heterocycl. Chem.* **11**, 93 (1974).

to product **187**. A comparable reaction with 3-aminocarbazole took place but it was not possible to determine in which direction the intramolecular acylation had occurred, although 9-tosyl-3-aminocarbazole underwent a comparable closure, and hydrolysis of the tosyl group gave the same tetracycle.³⁵⁸ Thermolysis of the azide **188** ($R^1 = H$ and Me; $R^2 = Me$ and $PhCH_2$) gave **189**.³⁵⁹



4. Oxy- and Aminoalkyl

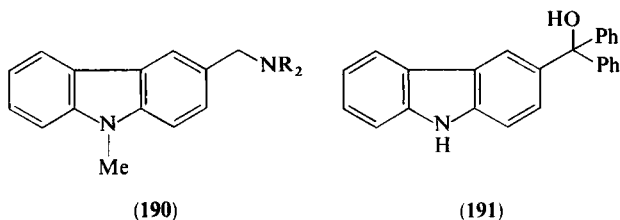
9-Methylcarbazole undergoes the Mannich reaction giving monosubstitution at the 3-position; **190** [$R_2 = (CH_2)_5$] was thus prepared.³⁶⁰ Condensation of carbazole itself with dichlorodiphenylmethane catalyzed by aluminium chloride gave the carbinol **191**.³⁶¹

³⁵⁸ M. Kulka and R. H. F. Manske, *J. Org. Chem.* **17**, 1501 (1952).

³⁵⁹ E. Bisagni, C. Ducrocq, J. M. Lhoste, C. Rivalle, and A. Civier, *J. C. S. Perkin Trans. I*, 1706 (1979).

³⁶⁰ J. Thesing and G. Semler, *Justus Liebigs Ann. Chem.* **680**, 52 (1964).

³⁶¹ H. Walba and G. E. K. Branch, *J. Am. Chem. Soc.* **73**, 3341 (1951).



5. Nitrogen

The best way to prepare 3-nitrocarbazole is by the nitration of 9-nitroso-carbazole in acetic acid followed by alkaline hydrolysis of the nitroso group.^{32,191,193} The 9-nitroso group must deactivate the system sufficiently to allow the mononitration product to be produced, but because it is not as electron withdrawing as an acyl group attack at C-2 is therefore not encouraged (see also Section II,A,4). Under more vigorous conditions carbazole itself undergoes dinitration to a mixture of 3,6- and 1,6-dinitro-derivatives.⁵⁰ A product believed to be 1,2,6,8-tetranitrocarbazole resulted from the sequential treatment of carbazole with hot, fuming sulfuric acid and then with hot 93% nitric acid.³⁶² Another report states that carbazole on treatment with 93% nitric acid gave 3,6-dinitrocarbazole at 70–80°C and 1,3,6,8-tetranitrocarbazole at 100°C.³⁶³ Copper(II) nitrate in acetic acid–acetic anhydride converted carbazole itself to the 3-monosubstituted carbazole, but it rather surprisingly converted 9-ethyl-, 9-propyl-, 9-butyl-, and 9-phenylcarbazoles to the 3,6-dinitro derivatives.³⁶⁴ However, 9-ethylcarbazole efficiently gave 3-nitro-9-ethylcarbazole using the acetic acid–nitric acid method.³⁶⁵ Tetranitromethane interacts with 9-phenyl-, 9-isopropyl-, and 9-vinylcarbazoles slowly in the absence of light but rapidly in its presence to give the corresponding 3-nitrocarbazoles. It has been suggested that light converts the charge transfer complex to the carbazole radical cation, NO_2 and $\text{C}(\text{NO}_2)_3$, recombination of which leads to the observed products.³⁶⁶ 3-Nitrocarbazole results from the hydrogen chloride–promoted rearrangement of 9-nitroso-carbazole; the 3-nitroso compound was said to be converted to **192** in water after 4 h.³⁶⁷ 4-Methyl-1-isopropyl-9-nitrosocarbazole on heating in petrol

³⁶² D. B. Murphy, F. R. Schwartz, J. P. Picard, and J. V. R. Kaufman, *J. Am. Chem. Soc.* **75**, 4289 (1953).

³⁶³ T. Amemiya, S. Fujii, and T. Horio, *Coal Tar (Tokyo)* **4**, 323 (1952) [*CA* **48**, 2034h (1954)].

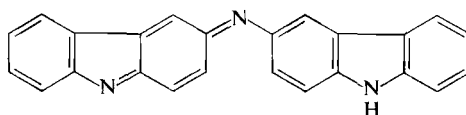
³⁶⁴ J. Pielichowski and A. Puszyński, *Monatsh. Chem.* **105**, 772 (1974).

³⁶⁵ G. Saint-Ruf, and B. Lobert, *Bull. Soc. Chim. Fr.*, 183 (1974).

³⁶⁶ D. H. Iles and A. Ledwith, *Chem. Commun.*, 364 (1969).

³⁶⁷ V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Tekhnol.* **15**, 1547 (1972) [*CA* **78**, 43188v (1973)].

with a trace of acetic acid also led to the introduction of a nitro group onto the ring at the 2- or 3- and 6- or 7-positions (mixture).¹⁹² 9-Nitrosocarbazole heated in xylene gave some 1-nitrocarbazole and a 30% yield of 3-nitrocarbazole. Oxidation with *m*-chloroperbenzoic acid led to 9-nitrocarbazole as well as 51% 1-nitrocarbazole and 13% 3-nitrocarbazole, whereas heating the 9-nitrosocarbazole in benzene gave 35% 1-nitrocarbazole and 52% 3-nitrocarbazole.²⁷⁸



(192)

Using nitric acid–acetic acid, 9-(2-hydroxyethyl)-,²¹³ 9-(2-chloroethyl),⁹² and 9-*n*-butylcarbazoles⁹⁴ have been mono-3-nitrated, whereas 9-carboxymethylcarbazole²¹⁵ gave a good yield of the 3,6-dinitro derivative.

In parallel with acylation (see Section II,D,3) nitration of 9-acetylcarbazole, with silver nitrate–aluminium chloride, leads to the introduction of the electrophile at C-2, thus providing 2-nitrocarbazole efficiently after hydrolysis of the N-substituent.⁶⁰ An early report that 9-tosylcarbazole is nitrated at C-1³⁶⁸ could not be repeated.³⁵⁸

Mild reaction conditions led to the displacement of a *tert*-butyl group from 1,3,6,8-tetra-*tert*-butylcarbazole and to the formation of 3-nitro-1,6,8-tri-*tert*-butylcarbazole along with a little 1-nitro-3,6,8-tri-*tert*-butylcarbazole.⁸⁵

Treatment of 1-bromocarbazole with sodium nitrite–acetic acid interestingly gave mainly 3-nitro-1-bromocarbazole.¹⁹² Fuming nitric acid converted 3-bromo-9-*n*-butylcarbazole to the 6-nitro derivative.⁹⁴ Nitration of 3,6-dibromo- and 3,6-dichlorocarbazole gave 1-nitro- and 1,8-dinitro-3,6-dihalocarbazoles as well as 1,6-dinitro-3-halo- and 1-nitro-3,6,8-trihalo-carbazoles.²⁷ 3,6-Dichlorocarbazole gave 4-nitro-3,6-dichlorocarbazole with concentrated nitric acid in acetic acid.³⁶⁹ Nitration of 3-nitro-9-(2-cyanoethyl)carbazole⁸⁸ and of 9-ethyl-3-formylcarbazole³⁴⁵ proceeds at C-6, the unsubstituted aromatic ring. 3,6,9-Triethylcarbazole gave a 1,8-dinitro derivative with acetic acid–fuming nitric acid at 0°C.³³¹

9-Methyl-2-acetamidocarbazole nitrated at C-3,³⁷⁰ and 9-ethyl-3-acetamidocarbazole nitrated at C-6³⁷¹; however 9-ethyl-3-formamido-, 9-ethyl-3-ethoxycarbamido-,³⁷¹ and 9-methyl-3-ethoxycarbamidocarbazoles³⁷⁰

³⁶⁸ B. K. Menon, and E. V. Menon, and D. H. Peacock, *J. Chem. Soc.*, 509 (1942).

³⁶⁹ K. Sugimoto, *Proc. Jpn. Acad.* **31**, 300 (1955) [*CA* **50**, 6049h (1956)].

³⁷⁰ E. Sawicki, *J. Am. Chem. Soc.* **76**, 664 (1954).

³⁷¹ J. C. Lancelot, J. M. Gazengel, and M. Robba, *J. Heterocycl. Chem.* **18**, 1281 (1981).

nitrated at C-4. Further nitration gave 4,6-dinitro and 4,6,8-trinitro derivatives.³⁷¹

It has long been recognized that carbazole couples with diazonium salts just once, at C-3, to give monoarylazo products.³⁷²⁻³⁷⁷ 9-Alkylcarbazoles react comparably. The use of sodium 4-dodecylbenzene sulfonate as a phase transfer catalyst was unsuccessful in an attempt to induce diazocoupling in both rings of 9-ethylcarbazole.³⁷⁷ 3,6-Dihydroxy-9-methylcarbazole likewise coupled only once, at C-2, with variously substituted benzene diazonium cations, whereas 3,6-dihydroxycarbazole itself coupled twice at 2- and 7-positions with α -naphthyl diazonium ion.³⁷⁸

6. Sulfur

The sulfonation of carbazole can proceed to a tetrasulfonic acid depending on conditions. Thus a mixture of 1,6- and 3,6-disulfonic acids can be obtained.³⁷⁹ More vigorous conditions lead to the 1,3,6-trisulfonic acid; this with oleum yields 2,3,6,8-tetrasulfonic acid, the orientation of the last introduced group being ascribed to sulfonation of the N-protonated trisulfonic acid.³⁸⁰ The same tetra acid is available directly from carbazole in high yield using oleum.³⁸¹

Chlorosulfonation of carbazole proceeds efficiently to the 3-monochlorosulfonyl derivative³⁸² in carbon tetrachloride or to the 1,3,6-trichlorosulfonylcarbazole by reaction in the presence of phosphorus pentoxide at 100°C.³⁸³ This latter process can be controlled by varying the proportions of chlorosulfonic acid and phosphorus pentoxide to produce 3,6-di-, 1,3,6-tri-, or 1,3,6,8-tetrachlorosulfonylcarbazoles.³⁸⁴

³⁷² H. Gilman and J. B. Honeycutt, *J. Org. Chem.* **22**, 562 (1957).

³⁷³ Z. J. Allan and J. Podstata, *Collect. Czech. Chem. Commun.* **25**, 1324 (1960).

³⁷⁴ Z. J. Allan and J. Podstata, *Collect. Czech. Chem. Commun.* **29**, 2264 (1964).

³⁷⁵ E. Heinrich, H. Kindler, and J. Ribka, German Patent 2,338,089 [CA **83**, P12171h (1975)].

³⁷⁶ E. Heinrich, H. Kindler, and J. Ribka, German Patent 2,212,755 [CA **79**, P147411z (1973)].

³⁷⁷ M. Ellwood, J. Griffiths, and P. Gregory, *J. C. S. Chem. Commun.*, 181 (1980).

³⁷⁸ V. I. Shishkina, L. A. Stephanova, and V. G. Mal'gina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **9**, 943 (1966) [CA **66**, 116672n (1967)].

³⁷⁹ V. F. Borodkin, *Zh. Prikl. Khim.* **24**, 1202 (1951) [CA **46**, 7092i (1952)].

³⁸⁰ P. P. Karpukhin and A. I. Levchenko, *Tr Khark. Politekh. Inst.* **4**, (2), 93 (1954) [CA **51**, 17876d (1957)].

³⁸¹ P. P. Karpukhin and O. I. Levchenko, *Khim. Promst. (Kiev)*, 18 (1963) [CA **59**, 7461c (1963)].

³⁸² V. I. Shishkina, T. I. Proshechkina, and L. H. Zubareva, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **13**, 269 (1970) [CA **73**, 45251f (1970)].

³⁸³ T. I. Proshechkina, V. I. Shishkina, N. D. Negodyaev, and G. M. Novikova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **12**, 903 (1969) [CA **72**, 31534t (1970)].

³⁸⁴ T. I. Proshechkina, V. I. Shishkina, V. F. Degtyarev, G. M. Novikova, and N. D. Negodyaev, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **12**, 1424 (1969) [CA **72**, 78793 (1975)].

Monothiocyanation of carbazole at 1- and 3-positions using thiocyanogen in acetic acid³⁸⁵ and of 9-methylcarbazole at C-3 using potassium thiocyanate in acetic acid have been recorded.³⁸⁶ This carbazole gave both 3-mono- and 3,6-dithiocyanatocarbazoles with potassium thiocyanate-bromine,³⁸⁷ and 9-nitrosocarbazole gave the 3,6-disubstituted product.³⁸⁷

Chorosulfonation of 3-nitrocarbazole occurred in the unsubstituted ring³⁸⁸ as did thiocyanation of 3-nitrocarbazole and 9-methyl-3-nitrocarbazole.³⁸⁹ Neither 1-nitrocarbazole nor its 9-methyl analog could be thiocyanated.³⁸⁹

Monosulfonation and disulfonation were observed with 3,6-dinitro-9-acetylcarbazole¹⁴⁹; 3,6-dinitrocarbazole gave the 1-substitution product. Chlorosulfonation of 3,6-dinitrocarbazole gave a mixture of mono- and dichlorosulfonyldinitro derivatives.³⁹⁰

7. Halogen

There is extensive literature⁷ on halogenocarbazoles prompted partly by searches for reagents and conditions whereby selective halogenations could be achieved. Reports vary probably because in some cases the major (or most easily isolated) product was reported as "the product"; in other work proportions of isomers were determined. It is worth recalling the use^{390a} of diazotized aminocarbazoles for the selective preparation of monohalocarbazoles.

Chlorination or bromination with the halogens in carbon disulfide gave good yields of the 3,6-dihalocarbazoles.^{27,391} In pyridine solution, bromine at 0°C and iodine at 70°C gave the 3-monohalocarbazoles³⁹¹; bromine in hot pyridine gave 3,6-dibromocarbazole and in hot acetic acid 1,3,6,8-tetrabromocarbazole.^{391a} Chlorine used in aqueous dispersion in the presence of

³⁸⁵ N. I. Baranova and V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **15**, 1678 (1972) [CA **78**, 111049c (1973)].

³⁸⁶ N. I. Baranova, V. I. Shishkina, and T. A. Galeeva, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **14**, 1054 (1971) [CA **75**, 140616d (1971)].

³⁸⁷ N. I. Baranova and V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **20**, 980 (1977) [CA **87**, 151948m (1977)].

³⁸⁸ V. I. Shishkina, G. M. Novikova, T. I. Vostnikova, and L. S. Gendler, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **15**, 86 (1972) [CA **76**, 140393z (1972)].

³⁸⁹ N. I. Baranova, L. N. Pushkina, and V. I. Shishkina, *Zh. Org. Khim.* **14**, 192 (1978) [CA **88**, 152349a (1978)].

³⁹⁰ G. M. Novikova, V. I. Shishkina, and N. T. Igonina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **17**, 1360 (1974) [CA **82**, 72722c (1975)].

^{390a} S. H. Tucker, *J. Chem. Soc.*, 1144 (1924).

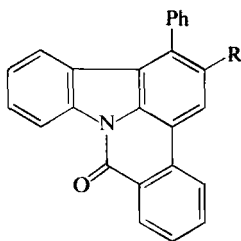
³⁹¹ M. Kuroki, *Kogyo Kagaku Zasshi* **70**, 63 (1967) [CA **68**, 12802e (1968)].

^{391a} J. Pielichowski and J. Kyziol, *Monatsh. Chem.* **105**, 1306 (1974).

a detergent such as sodium oleyl-*N*-methyltauriate was used to cleanly dihalogenate, thus producing 1,8-dichloro-3,6-dinitro- and 1,8-dichloro-9-ethyl-3,6-dinitrocarbazoles.³⁹²

Bromine in benzene or ethanol brings about 3,6-disubstitution of 9-vinylcarbazole as well as electrophilic addition to the double bond.^{234a} A good yield of 3-iodocarbazole results from the use of iodine-iodic acid in acetic acid at 70°C^{32,393}; iodine chloride in acetic acid caused 3,6-diiodination of 9-(2-chloroethyl)carbazole.¹¹⁷ 9-*n*-Butylcarbazole could be 3-monohalogenated with bromine in acetic acid at 0°C. This combination also allowed preparation of 6-bromo-9-alkyl-3-formylcarbazole^{343,345} and 6-bromo-9-isoamyl-3-nitrocarbazole.³⁴³

3,6-Dichlorocarbazole reacted with bromine in carbon tetrachloride at room temperature once only, at C-1, and at higher temperatures in carbon tetrachloride or acetic acid twice, at 1- and 8-positions.³⁹⁴ 9-*n*-Butyl-3-chlorocarbazole gave 1,6,8-tribromo-3-chloro-9-*n*-butylcarbazole with bromine in acetic acid at room temperature.⁹⁴ Iodine chloride in acetic acid produced 3-chloro-6-iodocarbazole from 3-chlorocarbazole.¹¹⁷ The bromine in pyridine substitution of 7-methoxy-1,4,9-trimethylcarbazole is instructive: 6-bromo-7-methoxy-1,4,9-trimethylcarbazole resulted.³¹⁴ Another instance where a choice of position for substitution was available was that of 1,4-diphenylcarbazole, which brominated in chloroform to give the 3,6-dibromo derivative. In contrast, **193** (R = H) with bromine in acetic acid at 80°C gave **193** (R = Br) as the only monosubstitution product.¹⁷¹



(193)

Sulfuryl chloride, though reported^{395,396} to give a complex mixture of mono-, di-, tri-, and tetrachlorinated products, has been recommended not only for the preparation of 3-chlorocarbazole^{32,112} and 9-ethyl-3-chloro-

³⁹² M. Erlenbach and W. Gelmroth, German Patent 887,197 (1953) [CA 52, P14696b (1958)].

³⁹³ H. Suzuki and Y. Tamura, *Nippon Kagaku Zasshi* **92**, 1021 (1971) [CA 76, 126650z (1972)].

³⁹⁴ V. Chmátal, Z. J. Allan, and F. Muzik, *Chem. Listy* **52**, 948 (1958); Z. J. Allan and J. Podstata, *Collect. Czech. Chem. Commun.* **24**, 2076 (1959).

³⁹⁵ J. Kyzioł and J. Pielichowski, *Rocz. Chem.* **51**, 815 (1977) [CA 87, 151935f (1977)].

³⁹⁶ V. P. Lopatinskii and I. P. Zharebtsov, *Izv. Tomsk. Politekh. Inst.* **198**, 73 (1974) [CA 83, 79018g (1975)].

carbazole¹¹² but also for 3,6-dichloro-,^{112,370} 3,6-dichloro-9-benzoyl-,³⁹⁷ 3,6-dichloro-9-acetyl,³⁹⁸ 3,6-dichloro-9-(2-hydroxyethyl)-,³⁹⁸ and 1,3,6,8-tetrachlorocarbazole.³⁹⁷ It has been used to 5-monochlorinate 3-nitrocarbazole³⁹⁷ and 1,3,6-trichlorinate 9-*n*-butylcarbazole⁹⁴ at 95°C and 3-monochlorinate 9-*n*-butylcarbazole at 0°C⁹⁴ and 6-monochlorinate 3-bromo-9-*n*-butylcarbazole.⁹⁴

N-Bromosuccinimide in the presence of benzoyl peroxide was used to prepare 3-bromocarbazole³² and 9-isobutyl-3-bromocarbazole,⁶³ to convert 3-chlorocarbazole to 3-chloro-6-bromocarbazole,¹¹⁷ and to convert 9-benzylcarbazole to a mixture of carbazole and 3-bromocarbazole, benzaldehyde also being formed.²¹²

Sulfur chloride-aluminium chloride converted carbazole to 1,2,3,4,5,6,7,8-octachlorocarbazole in moderate yield.³⁹⁹ The potassium bromide-potassium bromate combination 3-monobrominates 9-ethylcarbazole.³⁵⁰

E. REACTIONS INVOLVING C-SUBSTITUENTS

1. *Alkyl and Hydroxyalkyl*

Removal of *tert*-butyl groups from carbazole ring positions by strong acid or Lewis acid catalysis has been used to transform 2-*tert*-butyl-, 2-*tert*-butyl-4-methyl-, 7-*tert*-butyl-4-methyl-,⁴⁰⁰ 2,7-di-*tert*-butyl-,⁴⁰¹ and 2,7-di-*tert*-butyl-4-methylcarbazoles into carbazole and 4-methylcarbazole, respectively. 1,3,6,8-Tetra-*tert*-butylcarbazole partially dealkylates with concentrated sulfuric acid at room temperature to give a mixture of 1,3,6-tri- and 3,6-di-*tert*-butylcarbazoles.⁸⁵ 1-Methylcarbazole loses its substituent at 850°C.⁴⁰²

Mono side-chain bromination of a carbazole 3-methyl group was achieved using bromine-light after reducing the susceptibility of the ring to electrophilic bromination by first introducing a 9-phenylsulfonyl group,¹⁹⁸ although side-chain bromination of 3-methyl-1-methoxycarbazole with *N*-bromosuccinimide-benzoyl peroxide was apparently achieved without this

³⁹⁷ V. P. Lopatinskii, I. P. Zhrebtssov, and S. F. Zelinskaya, *Izv. Tomsk. Politekh. Inst.* **167**, 111 (1967) [*CA* **68**, 49393y (1968)].

³⁹⁸ V. P. Lopatinskii, I. P. Zhrebtssov, L. I. Kuznetsova, and V. S. Gorshkova, *Izv. Tomsk. Politekh. Inst.* **163**, 18 (1970) [*CA* **75**, 118191q (1971)].

³⁹⁹ C. Glidewell and J. C. Walton, *J. C. S. Chem. Commun.*, 915 (1977).

⁴⁰⁰ M. Tashiro and T. Yamoto, *Kenkyu Hokoku-Asahi Garasu Kogyo Gijutsu Shoreikai* **36**, 93 (1980) [*CA* **95**, 24711v (1981)].

⁴⁰¹ M. Tashiro and T. Yamoto, *Synthesis*, 48 (1979).

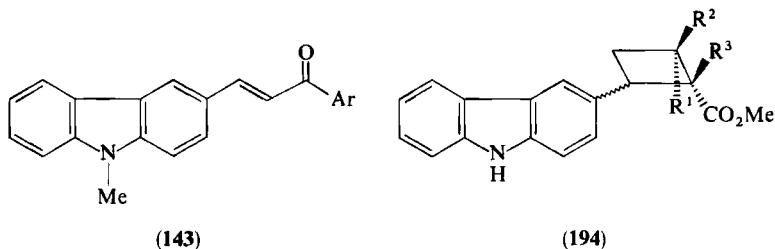
⁴⁰² R. F. C. Brown and M. Butcher, *Aust. J. Chem.* **75**, 149 (1972).

precaution.⁴⁰³ The 3-bromomethylcarbazole was transformed by standard means into 3-(2-carboxyethyl)carbazole,¹⁹⁸ and the 1-methoxy-3-bromomethylcarbazole was hydrolyzed and manganese dioxide oxidized to 1-methoxy-3-formylcarbazole.⁴⁰³ 2-Hydroxymethyl-1-methylcarbazole was converted to the 2-aldehyde most efficiently with chromium trioxide.⁴⁰⁴

There seem to be no examples of carbazole alkyl groups being oxidized directly to carboxylic acid groups. Dichlorodicyano-*p*-benzoquinone has been used to oxidize a methyl group to aldehyde in 3-methyl-2,6-dimethoxycarbazole⁴⁰⁵ and 3-methyl-2,6,7-trimethoxycarbazole.⁴⁰⁶ 3,3'-Dicarbazolylmethanes are particularly easy to oxidize by tritylcarbonium ions with effective loss of hydride from the methylene group, producing blue cations.^{186,296,297} Sodium hydroxide-iodine degradation of 1-methyl-2-acetonyl-carbazole produced the carbazole-2-acid.³⁵³

2. Alkenyl

Examples of ozonolysis of double bonds directly attached to the carbazole 2-position show that such processes proceed normally with no disruption of the heterocyclic system.^{353,407} 9-Ethyl-3-vinylcarbazole undergoes cycloaddition reactions to give cyclobutanes **194** ($R^1 = R^2 = R^3 = \text{CO}_2\text{Me}$; $R^1 = \text{H}$, $R^2 = \text{CO}_2\text{Me}$, $R^3 = \text{CN}$; $R^1 = \text{H}$, $R^2 = R^3 = \text{CO}_2\text{Me}$).⁴⁰⁸ The unsaturated ketones **143** epoxidized normally with alkaline hydrogen peroxide.³⁰¹



3. Acyl

a. Aldehydes. Most studies have been conducted with carbazole-3-aldehydes because these are most easily made. The reactions of carbazole aldehydes show them to be typical aromatic aldehydes. 3-Formyl- and 3-

⁴⁰³ D. P. Chakraborty and B. K. Chowdhury, *J. Org. Chem.* **33**, 1265 (1968).

⁴⁰⁴ J. P. Kutney and D. C. Grierson, *Heterocycles* **3**, 171 (1975).

⁴⁰⁵ R. B. Sharma and R. S. Kapil, *Chem. Ind. (London)*, 158 (1980).

⁴⁰⁶ R. B. Sharma, R. Sethverma, and R. S. Kapil, *Experientia* **36**, 815 (1980).

⁴⁰⁷ G. Buchi and E. Warnhoff, *J. Am. Chem. Soc.* **81**, 4433 (1959).

⁴⁰⁸ M. Abdelkader and H. K. Hall, *J. Org. Chem.* **47**, 292 (1982).

formyl-9-alkylcarbazoles undergo Wolff Kischner reduction^{32,313,341,343,345,403,409} to the corresponding methylcarbazoles and borohydride^{186,296} reduction to the carbinols. However, during the course of the synthesis of the complete set of mono- and dimethylcarbazoles, attempted Huang–Minlon reduction of 2,3-dimethyl-6-formyl-, 1,4-dimethyl-3,6-diformyl-, and 2,4,6-trimethyl-3-formylcarbazoles brought about decarbonylation.³⁴¹ Loss of a 3-formyl group also occurred during removal of a 9-ethyl, using sulfur at 300°C,²⁰⁹ and 3-ethyl-1-methyl-2-formylcarbazole was decarbonylated by heating.⁴⁰⁷ 3-Formyl-2-hydroxy-8-methoxycarbazole was reduced to the 3-methyl derivative using hydrogen–palladium/charcoal.³⁰⁵ 1-Methyl-2-formylcarbazole was oxidized to 1-methylcarbazol-2-ylcarboxylic acid with potassium permanganate.³⁵³

Aldol and aldol-type condensations of 1-methyl-2-formylcarbazole with acetone,³⁵³ of 9-methyl-3-formylcarbazole with aryl methyl ketones,⁴¹⁰ of 1,4-dimethyl-2-³⁵⁴ and 9-ethyl-3-formylcarbazoles³⁵⁶ with nitromethane, of 9-methyl-3-formylcarbazole with aliphatic esters,⁴¹¹ and finally of 9-ethyl-3-formylcarbazole twice with dialkylketones (i.e., on both sides of the carbonyl group),⁴¹² with 1,3-diketones three times,⁴¹² with 1,2-dimethylbenzoxazolium and -thiazolium iodides,⁴¹³ and with arylacetonitriles³⁴⁵ have been recorded. Carbazole-2- and -3-aldehydes have been made to undergo the Knoevenagel reaction with malonic acid,^{359,412} and 9-ethyl-3-formylcarbazole has been made to condense with malononitrile.³⁴⁴ 9-Methyl-3-formylcarbazole undergoes the Wittig reaction with triphenylphosphonium arylmethylides.¹³⁸

9-Alkyl-3-formylcarbazoles form arylhydrazones^{345,414–416} and azines or hydrazones with hydrazine.^{193,414} 9-Ethyl-3-formylcarbazole gives Schiff bases with arylamines.⁴¹⁷ Various substituted 3-formylcarbazoles condense with aminoacetal,^{313,315–321} and the resulting imines are easily reduced catalytically³¹³ or with sodium borohydride.^{316,318–321} Anils from

⁴⁰⁹ P. Bruck, *Chem. Commun.* 1690 (1970); Y. Murakami and H. Ishii, *Chem. Pharm. Bull.* **29**, 699 (1961); for a revised view on the mechanism see Y. Murakami and N. Okuyama, *Tetrahedron Lett.* **24**, 2189 (1983).

⁴¹⁰ V. M. Nikitchenko, G. S. Vodotyka, V. M. Voronkin, and V. F. Lavrushin, *Ukr. Khim. Zh. (Russ. Ed.)* **42**, 845 (1976) [*CA* **86**, 29570x (1977)].

⁴¹¹ L. Zheljazkov, K. Faitondjieva, M. Dimitrova, S. Spassov, and M. Palamereva, *Justus Liebig's Ann. Chem.*, 150 (1979).

⁴¹² G. Saint-Ruf and Ng. Ph. Buu-Hoi, *Bull. Soc. Chim. Fr.*, 2753 (1969).

⁴¹³ H. Depoorter and J. R. Schellekens, German Patent 2,423,587 [*CA* **83**, P113198g (1975)].

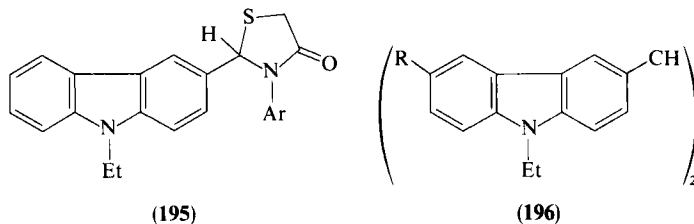
⁴¹⁴ M. N. Popova and V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **14**, 1681 (1971) [*CA* **76**, 140398e (1972)].

⁴¹⁵ H. Y. Aboul-Enein, D. W. Fattig, and R. L. Settino, *Can. J. Pharm. Sci.* **8**, 65 (1973).

⁴¹⁶ M. N. Popova, V. M. Kurilenko, L. P. Basova, and V. I. Shishkina, *Khim.-Farm. Zh.* **7**, 14 (1973) [*CA* **80**, 14807g (1974)].

⁴¹⁷ Ng. Ph. Buu-Hoi, G. Saint-Ruf, J. C. Perche, and J. C. Bouvgeade, *Chim. Ther.* **3**, 110 (1968).

9-ethyl-3-formylcarbazole add thioglycollic acid generating heterocycles **195**.⁴¹⁷ Reductive amination of 9-methyl-3-formylcarbazole produces 9-methyl-3-dimethylaminomethylcarbazole.³⁶⁰ The azines formed from 9-ethyl- and 9-ethyl-6-methyl-3-formylcarbazoles lose nitrogen on sublimation, generating the alkenes **196** (R = H or Me).⁴¹⁸



b. *Ketones*. Carbazole ketones behave in most instances as normal aryl ketones. They can be reduced to the alkane by the Wolff Kischner method^{119,331,332}. The Clemmensen method was applied successfully to 3,6-diphenacetylcarbazole,¹¹⁸ and hydrogen–nickel was used to reduce 3-benzoylcarbazole.³³⁰ Application of the Meerwein–Pondorff–Varley procedure with aluminium isopropoxide can give rise to the alcohol, to the isopropyl ether of the corresponding alcohol,⁴¹⁹ or to the dehydration product of the alcohol, the alkenylcarbazole.^{63,259,420–422} 3- and 2-Vinyl-substituted carbazoles have been made in this way. Partial loss of a 3-acetyl group has occurred during 9-de-ethylation using sulfur at 300°C.²⁰⁹

Hypobromite⁴²³ and hypoiodate³²⁸ oxidize 3,6-diacetylcarbazoles to the diacids. Molten potassium hydroxide converts carbazole-2-mono- and carbazole-3-mono- and 3,6-diphenacetylcarbazoles to the corresponding mono- and dicarboxylic acids.¹¹⁸ The cleavage of 3-isobutyryl carbazoles with potassium *tert*-butoxide in dimethyl sulfoxide in the presence of air is accompanied by chemiluminescence.³²⁷

9-Methyl-3,6-diacetylcarbazole undergoes a double aldol condensation with aromatic aldehydes.⁴²⁴ The cyclic ketone **197** (R = H₂) condenses with

⁴¹⁸ Ng. Ph. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 955 (1967).

⁴¹⁹ V. P. Lopatinskii and E. E. Sirotkina, *Izv. Tomsk. Politekh. Inst.* **126**, 67 (1964) [*CA* **64**, 3457g (1966)].

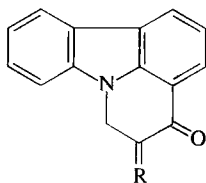
⁴²⁰ V. P. Lopatinskii and E. E. Sirotkina, *Izv. Tomsk. Politekh. Inst.* **136**, 181 (1965) [*CA* **65**, 16930c (1966)].

⁴²¹ V. P. Lopatinskii and E. E. Sirotkina, *Metody Poluch. Khim., Reakt. Prep.* **11**, 40 (1964) [*CA* **65**, 2203c (1966)].

⁴²² V. P. Lopatinskii, E. E. Sirotkina, and S. D. Pukhal'skaya, *Izv. Tomsk. Politekh. Inst.* **148**, 70 (1967) [*CA* **70**, 87441m (1969)].

⁴²³ N. D. Negodyaev and Z. V. Pushkareva, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 46 (1966) [*CA* **65**, 2198c (1966)].

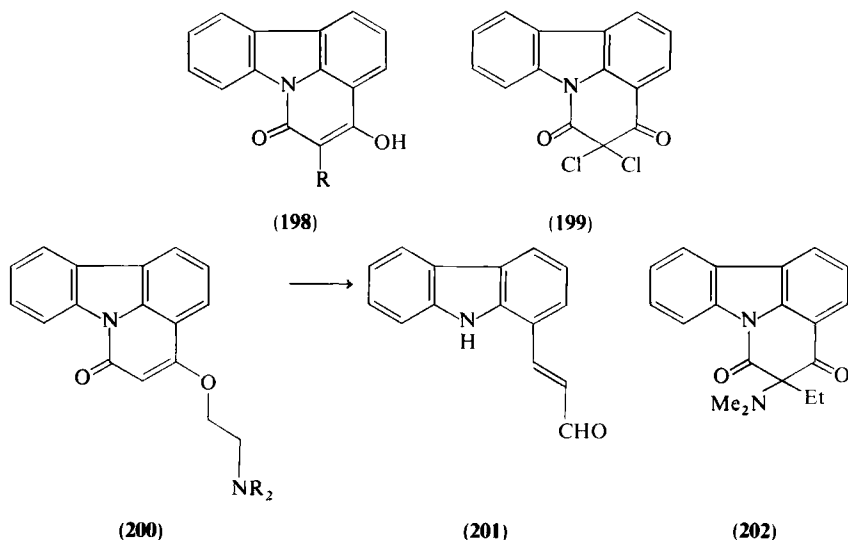
⁴²⁴ V. M. Nikitchenko, S. Ibragim, and V. F. Lavrishin, *Ukr. Khim. Zh. (Russ. Ed.)* **39**, 368 (1973) [*CA* **79**, 5209r (1973)].



(197)

aromatic aldehydes producing **197** ($R = \text{CH}-\text{Ar}$) or with 4-dimethylaminonitrosobenzene giving **197** ($R = N-\text{C}_6\text{H}_4-p\text{-NMe}_2$).²²⁰ Mannich condensation α to carbonyl in carbazole ketones proceeds normally in acid solution; in neutral or basic solution reaction takes place instead at the carbazole nitrogen, if available.¹⁸⁵

The chlorination⁴²⁵ of **198** ($R = \text{H}$), available via the debenzoylation of **198** ($R = \text{CH}_2\text{Ph}$) with phenol,¹⁷² produces the dichloride **199**.⁴²⁵ Mild alkali treatment of the dichloride produces 1-dichloroacetylcarbazole, zinc-acetic acid reduction of which gave 1-acetylcarbazole in high yield.⁴²⁶ More vigorous alkaline cleavage of the dichloride produced carbazol-1-ylcarboxylic acid, also very efficiently.⁴²⁷ O-Alkylation of **198** ($R = \text{H}$) with 2-dialkylamino-ethyl halides produced ethers **200**, and lithium aluminium hydride reduction of **200** ($R = \text{Et}$) gave aldehyde **201**.⁴²⁸ Finally, in this intriguing



⁴²⁵ E. Ziegler and Th. Kappe, *Monatsh. Chem.* **94**, 447 (1963).

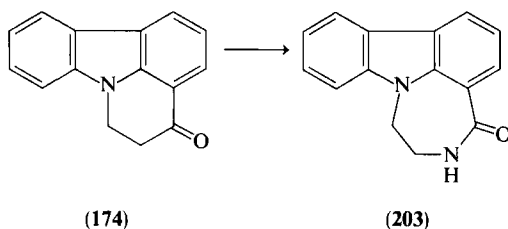
⁴²⁶ Th. Kappe and E. Ziegler, *Monatsh. Chem.* **94**, 935 (1963).

⁴²⁷ E. Ziegler and Th. Kappe, *Monatsh. Chem.* **94**, 736 (1963).

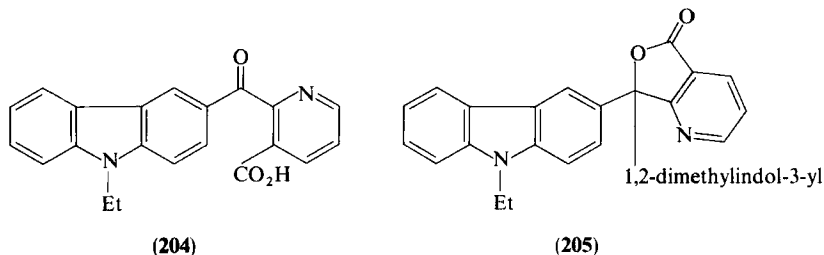
⁴²⁸ E. Ziegler, U. Rossmann, F. Litvan, and H. Meier, *Monatsh. Chem.* **93**, 26 (1962).

series, bromination of the ethyl homologs **198** ($R = Et$), displacement of halogen with dimethylamine, and lithium aluminium hydride treatment of **202** allowed the production of 1-formylcarbazole.¹⁷³

3-Acetylcarbazole⁴²⁹ and 9-ethyl-3-propionylcarbazole³³¹ underwent normal Wilgerodt reactions. The ketone **174** reacted with sodium azide–polyphosphoric acid with migration of the alkyl substituent generating lactam **203**.³³⁴



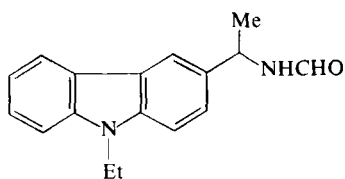
1,2-Dimethylindole condensed with keto acid **204** in the presence of acetic anhydride forming **205**.³⁴⁰ The formation of the oxime and subsequent Beckmann rearrangement of 2-acetyl- or 2,9-diacetylcarbazoles provides a good method for making 2-aminocarbazoles.⁶¹ Leuckart reactions of various 3-acylcarbazoles have been achieved: 9-ethyl-3-acetylcarbazole reacted with formamide producing **206**.⁴³⁰ 3-Acetylcarbazole and N,N' -diarylthioureas at high temperatures produce quinolylcarbazoles, for example a compound accorded structure **207** from the diphenylthiourea.⁴³¹



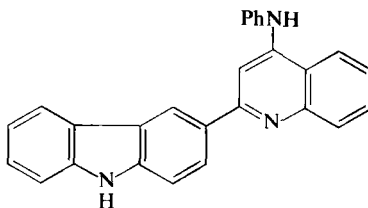
⁴²⁹ M. M. Sukhoroslova, V. P. Lopatinskii, E. E. Sirotkina, L. P. Levchenko, and T. F. Turchina, *Izv. Tomsk. Politekh. Inst.* **198**, 75 (1974) [*CA* **83**, 58587b (1975)].

⁴³⁰ E. E. Sirotkina, V. P. Lopatinskii, L. F. Kovaleva, and O. G. Yakushina, *Izv. Tomsk. Politekh. Inst.* **250**, 164 (1975) [*CA* **86**, 72355t (1977)]; L. F. Kovaleva, E. E. Sirotkina, V. P. Lopatinskii, V. M. Kurilenko, L. P. Basova, N. A. Ledeneva, U. K. Kiselev, I. B. Abaza, and O. A. Malyuga, *Khim.-Farm. Zh.* **8**, 6 (1974) [*CA* **81**, 37452x (1974)]; E. E. Sirotkina, L. F. Kovaleva, V. P. Lopatinskii, V. M. Kurilenko, and L. P. Basova, *Tezisy Dokl.—Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop.*, 2nd, 1973, 79 (1973) [*CA* **85**, 177187x (1976)].

⁴³¹ J. Moszew and S. Sulko, *Rocz. Chem.* **5**, 169 (1951) [*CA* **46**, 7102h (1952)].



(206)



(207)

c. *Carboxylic Acids.* As before, there are only rare deviations from normal arylcarboxylic acid chemistry. Straightforward esterification^{423,432} via acid chloride formation^{351,423,432} or with diazomethane⁴³³ as well as alkaline saponification of esters,^{351,433,434} lactones,³⁵⁵ and nitriles⁴³³ have been achieved. Reduction of a 3-cyano group with hydrogen nickel was straightforward.³⁵⁴ A 2-acid chloride has been reacted with diazomethane and then transformed into the acetamide by the Wolff rearrangement.³⁵¹ Carbazole-2-esters are reduced normally with lithium aluminium hydride,^{351,354,404} but the ester in methyl 1,4-dimethyl-carbazol-3-ylcarboxylate was fully reduced by this reagent giving 1,3,4-trimethylcarbazole.³⁵⁴ A 1-acid chloride was converted to its *N*-methylhydrazide.¹⁷⁰

There is a greater tendency for decarboxylation of carboxyl groups at the carbazole 1-position than at the other positions; for example, 9-methylcarbazole-1,2,3,4-tetracarboxylic acid heated with soda lime lost only the 1-carboxyl group (as well as the *N*-methyl group).⁵³ If one assumes that anionic character develops on the carbon from which the carboxyl group departs, then the easier loss of a 1-carboxyl fits appropriately with the known position of deprotonation (see Section II,A,3). All four carboxyl groups and the 9-methyl, if present, can be cleaved from a carbazole-1,2,3,4-tetra acid on dry distillation.⁴³³ 4-Methyl-carbazol-3-ylcarboxylic acid (**208**) was decarboxylated on heating with copper powder in quinoline.⁴³⁴ 9-Ethyl-3-cyanocarbazole gave the tetrazole **209** with sodium azide.⁴³⁶ Carbazole-2,3-diester condense with hydrazine to give the tetracycles **210** (R^1 and $R^2 = H$ or alkyl).⁴³⁷ In a classic, systematic study each of the four isomeric carbazole

⁴³² N. D. Negadyaev and Z. V. Pushkareva, *Khim. Geterotsikl. Soedin.*, 586 (1966) [*CA* **66**, 28605n (1967)].

⁴³³ W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Am. Chem. Soc.* **81**, 6010 (1959).

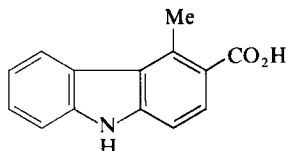
⁴³⁴ T. Sakau, S. Matsubara, H. Takagi, Y. Tokunaga, and T. Miwa, *Tetrahedron Lett.*, 4925 (1968).

⁴³⁵ D. P. Chakraborty and B. K. Chowdhury, *J. Indian. Chem. Soc.* **48**, 225 (1971).

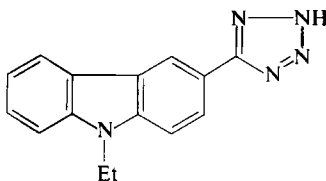
⁴³⁶ M. Okazaki, Japan Patent 77/139,063 [*CA* **88**, P152623k (1978)].

⁴³⁷ M. Robba, H. Landelle, M. Cugnon de Sevrécourt, and D. Laduree, *C. R. Hebd. Seances Acad. Sci., Ser. C* **282**, 635 (1976).

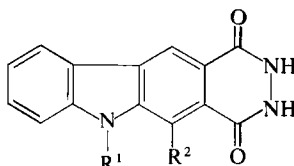
aldehydes was prepared from the corresponding methyl esters using the McFadyens-Stevens sequence.⁴³⁸



(208)



(209)



(210)

4. Nitrogen

The reduction of carbazole nitro groups to the primary amines is straightforward: stannous chloride,^{92,193,369,370} tin-hydrochloric acid,⁴³⁹ iron-hydrochloric acid⁴⁴⁰ hydrogen-palladium/charcoal,⁴³⁹ hydrogen-nickel,^{50,85,135,371,441} hydrazine-palladium,⁶⁰ and hydrazine-nickel³³¹ have all been employed. 3,6-Dichloro-1,8-dinitrocarbazole was partially reduced with sodium hydrogen sulfide to give 1-amino-8-nitro-3,6-dichloro-carbazole.³⁹⁴

Aminocarbazoles are typical aromatic amines: 3-aminocarbazoles, which are the most studied, form Schiff bases with aromatic aldehydes,^{92,441,442} and ketones.⁴⁴³ Use was made of such a benzaldehyde imine by methylation with dimethyl sulfate and then by hydrolysis with acid to produce the mono-N-methylated amine.⁹² The dimethylated material was obtained via the trimethylammonium iodide, which gave 3-dimethylaminocarbazole on

⁴³⁸ P. H. Carter, S. G. P. Plant, and M. Tomlinson, *J. Chem. Soc.*, 2210 (1957).

⁴³⁹ S. Natori, M. Ito, and T. Nakagome, *Pharm. Bull.* **5**, 548 (1957).

⁴⁴⁰ N. Kuroki and K. Konishi, *J. Soc. Org. Synth. Chem. Tokyo* **12**, 29 (1954) [*CA* **51**, 723c (1957)].

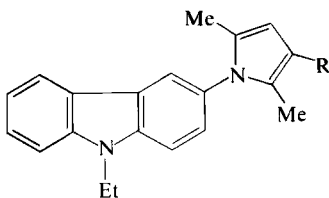
⁴⁴¹ J.-C. Lancelot, J.-M. Gazengel, S. Rault, and M. Robba, *Chem. Pharm. Bull.* **30**, 1674 (1982).

⁴⁴² T. N. Kulikova, V. I. Shishkina, and I. P. Ryazanov, *Khim. Geterotsikl. Soedin.*, 1353 (1970) [*CA* **74**, 53403t (1971)]; N. S. Kozlov, T. P. Shulyat'eva, and U. V. Misenzhinikov, *Katal. Prevrashch. Org. Soedin.*, 67 (1973) [*CA* **84**, 17061c (1976)]; S. G. Levina, T. M. Kulikova, V. I. Shishkina, and I. I. Kalinichenko, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **21**, 485 (1978) [*CA* **89**, 107263c (1978)].

⁴⁴³ C. S. Sheppard and M. H. Wilt, U.S. Patent 3,041,348 [*CA* **58**, P3399d (1963)].

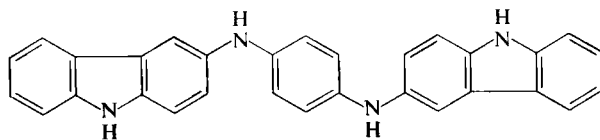
heating at 200°C.⁹² However, another report states that 3-aminocarbazole can be converted to its dimethyl derivative with dimethyl sulfate-sodium hydroxide, apparently without either additional side chain or 9-methylation.¹¹⁰ Trimethyl phosphate can also be used for this purpose.³² Hydrogenation of cyclohexanone imines gave the cyclohexylamino carbazoles.⁴⁴³ 9-Ethyl-3-aminocarbazole was arylated on the amino group on reaction with α - or β -naphthol in the presence of iodine, giving the 3-naphthylamino derivatives.³⁰⁷

3-Aminocarbazoles form 3-(pyrrol-1-yl)carbazoles with 1,4-dicarbonyl compounds.^{441,444} It is interesting that Vilsmeier formylation of one such pyrrolylcarbazole (**211**: R = H), in which attack could occur at a pyrrole β -position or on the unsubstituted carbazole ring at C-6, substitution took the former course, thus producing **211** (R = CHO).⁴⁴⁴ 3-Aminocarbazole gave an imide with maleic anhydride.¹⁹³

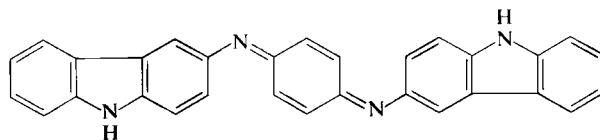


(211)

When cyclohexane-1,4-dione reacted with 3-aminocarbazole, the presumed initial double condensation product was dehydrogenated and **212** was actually isolated. Dichromate oxidation of this diamine gave the quinone



(212)

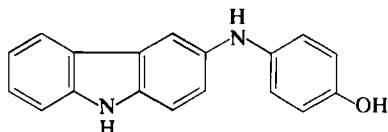


(213)

⁴⁴⁴ J. C. Perche and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 1117 (1974).

⁴⁴⁵ H. J. Teuber and L. Vogel, *Chem. Ber.* **103**, 3319 (1970).

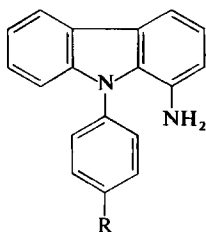
imine **213**.⁴⁴⁵ The same amine was reacted with hydroquinone in the presence of iodine, but in the absence of oxygen, to give 3-(4-hydroxyphenyl-amino)carbazole (**214**).⁴⁴⁶



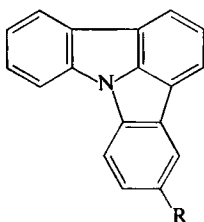
(214)

Normal acylation of carbazole amines and diamines, without reaction at the ring nitrogen, has been reported.^{110,369,370,441} Such amides can be easily hydrolyzed back to amine.^{369,370} Displacement by carbazole amino groups of halogen from activated aromatic and heteroaromatic compounds also occurs without involvement of the ring nitrogen.^{447,448}

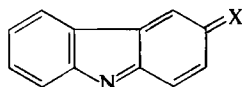
Carbazole-1- and carbazole-3-amino groups have been diazotized,^{32,135,311,312,386,449} and the diazonium salts coupled with 1,3-diketones⁴⁴⁹ and ethyl acetoacetate,³¹² used in Sandmeyer reactions,^{32,85,386} reduced to the hydrazines³¹¹ and made to effect intramolecular arylation of a 9-aryl group, such as in the transformation of **215** (R = Me or CO₂Me) into **216** (R = Me or CO₂Me).¹³⁵ It is worth repeating the earlier observation



(215)



(216)

(217) X = N₂

(218) X = NH

that ammonia at 0°C converts carbazole-3-diazonium chloride to light-sensitive red crystals of **217**; this material coupled with β -naphthol to give the same derivative as obtained with the conventional use of the diazonium

⁴⁴⁶ S. Piesch, F. Engelhardt, H. Wille, W. Weidemueller, and A. Meyer, German Patent 2,900,441 [CA 93, P186165f (1980)].

⁴⁴⁷ S. S. Berg and V. Petrow, *J. Chem. Soc.*, 784 (1952).

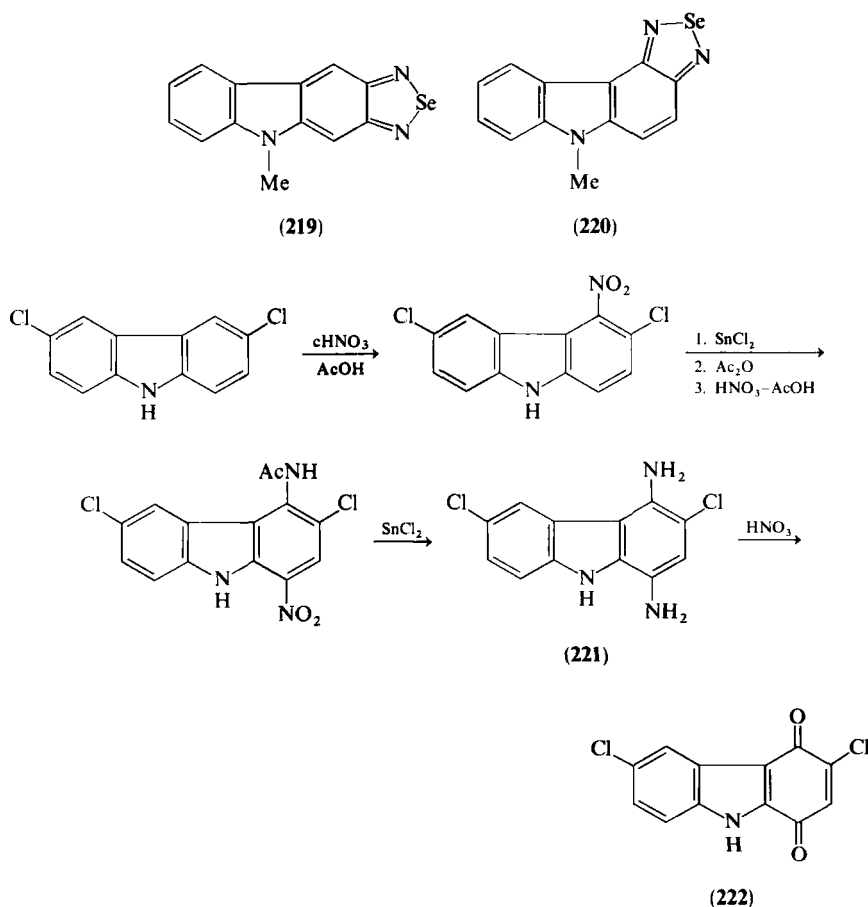
⁴⁴⁸ Z. Yoshida, Y. Kato, and R. Oda, *J. Chem. Soc. Jpn., Ind. Chem. Sect.* **56**, 411 (1953) [CA 49, 6910i (1955)].

⁴⁴⁹ M. N. Popova, V. I. Shishkina, and L. P. Kislitsyna, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **16**, 1051 (1973) [CA 79, 105034y (1973)].

⁴⁵⁰ G. T. Morgan and H. N. Read, *J. Chem. Soc.*, 2709 (1922).

chloride.⁴⁵⁰ Other examples of the coupling of carbazole diazonium salts have been described.^{85,451} The diazotization of 3,6-diaminocarbazole produced **218** after leaving the solution for 2 days at 0–4°C and then warming at 50–60°C when nitrogen was evolved.⁴⁵²

Hydrogenolysis of 4-phenylazocarbazole⁴⁵³ or 4-azidocarbazole⁴⁵⁴ gave 4-aminocarbazole. 9-Methylcarbazole-2,3- and -3,4-diamines reacted with selenium dioxide to produce the selenadiazoles **219** and **220**, respectively.³⁷⁰



⁴⁵¹ Z. V. Pushkareva and S. I. Omel'chenko, *Zh. Prikl. Khim.* **32**, 467 (1959) [*CA* **53**, 13134b (1959)].

⁴⁵² V. I. Shishkina, N. S. Klubnikina, and K. V. Aglitskaya, *Khim. Geterotsikl. Soedin.*, 645 (1969) [*CA* **72**, 66734k (1970)].

⁴⁵³ P. Spagnolo, A. Tundo, and P. Zanirato, *J. Org. Chem.* **42**, 292 (1977).

⁴⁵⁴ J. H. Boyer and G. J. Mikol, *Chem. Commun.*, 734 (1969).

Oxidation with nitric acid–acetic acid converted the diamine **221** to the quinone **222**.³⁶⁹

5. Sulfur

The aqueous acidic hydrolysis of carbazolesulfonic acids has been studied; their resistance to hydrolysis increases with the number of sulfonic acid groups on the nucleus, thus 3,6-di- < 1,3,6-tri- < 1,3,6,8-tetrasulfonic acids in terms of stability to aqueous acid. It was also demonstrated that 2,7-di- > 3,6-di- > 1,6-disulfonic acids in terms of lability.⁴⁵⁵ Carbazole sulfonyl chlorides form sulfonamides with arylamines.⁴⁵⁶

3-Hydroxycarbazole has been prepared by heating the 3-sulfonic acid with strong alkali,⁴⁵⁷ and its 2-isomer has been prepared by converting the 2,3,6,8-tetra acid to 2-hydroxycarbazole-3,6,8-trisulfonic acid with hot alkali and then aqueous acidic removal of the three residual sulfonic acid groups.³⁸¹

The 3-thiocyanato- and 3,6-dithiocyanatocarbazoles were reduced to the thiols with sodium sulfide,⁴⁵⁸ carbazole thiols can be S-alkylated in the usual way without interference from carbazole nitrogen.^{386,458} 9-Methyl-3-thiocyanatocarbazole was reduced to the thiol with zinc–hydrochloric acid.³⁸⁶ 9-Methyl-3-thiocyanatocarbazole in 50% aqueous acetic acid at room temperature gave the 3,3'-dicarbazolyldisulfide.³⁸⁶

6. Halogen

Iodine at the N-alkylcarbazole 3-position has been reductively removed with lithium aluminium hydride^{186,296} and hydrogen–Raney nickel,⁸⁵ and bromine at the same position has been removed with lithium-*tert*-butanol.¹⁸⁶ Hydrogen–nickel at 600 psi has also been used to hydrogenolyze carbazole carbon–bromine bonds,⁴⁵⁹ and hydrogen–palladium/charcoal at 200°C to remove a 1-chlorine.⁴⁶⁰

⁴⁵⁵ V. F. Borodkin, *Tr. Ivanov. Khim.-Tekhnol. Inst.* **5**, 194 (1956) [*CA* **54**, 17396e (1960)].

⁴⁵⁶ T. I. Proshechkina, V. I. Shishkina, T. V. Mikhailova, and V. V. Kazakova, *Khim.-Farm. Zh.* **3**, 9 (1969) [*CA* **71**, 101642g (1969)].

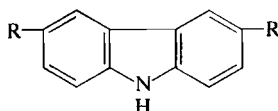
⁴⁵⁷ L. A. Stepanova and V. I. Shishkina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **10**, 298 (1967) [*CA* **67**, 73475b (1967)].

⁴⁵⁸ N. I. Baranova and V. I. Shishkina, *Khim. Geterotsikl. Soedin.* **7**, 1076 (1971) [*CA* **76**, 34051b (1972)].

⁴⁵⁹ R. B. Carlin and G. W. Larson, *J. Am. Chem. Soc.* **79**, 934 (1957).

⁴⁶⁰ J. A. Cummins and M. L. Tomlinson, *J. Chem. Soc.*, 3475 (1955).

The halogen in 3-bromocarbazole was displaced by methoxyl using sodium methoxide and copper(I) catalysis.⁴⁶¹ Apparently no such catalysis was necessary to displace the bromine of 9-methyl-3-bromocarbazole with phenylhydrazine, the aromatic nitrogen being the nucleophilic site of the hydrazine.⁴⁶² 3-Mono- and 3,6-dibromocarbazoles were converted to the mono- and dinitriles using copper(I) cyanide in pyridine.³² Both halogens of 3,6-di-iodocarbazole were displaced by carbon on coupling with phenylacetylene, producing **223**.⁴⁶³ Palladium(II) acetate effected coupling between styrene, and both 3- and 6-positions of 3,6-dibromocarbazole generating the 3,6-distyrylcarbazole **224**.⁴⁶⁴



(**223**) R = PhC≡C

(**224**) R = PhCH=CH

9-Ethyl-3-lithiocarbazole generated from the bromide and butyllithium reacted with chlorotriphenylsilane³⁵⁰ and chlorotrimethylsilane,⁵⁷ to produce the 3-triphenylsilyl³⁵⁰ and 3-trimethylsilyl⁵⁷ derivatives; it reacted twice with dichlorodiphenylsilane and three times with trichlorophenylsilane to give the corresponding dicarbazol-3-yl-diphenylsilane and tricarbazol-3-yl-phenylsilane, respectively.³⁵⁰ Conversely, triphenylsilyl-potassium or -lithium displaced the bromine of 9-ethyl-3-bromocarbazole to give the 3-triphenylsilylcarbazole.^{350,465} Reaction of the 3-lithiated-9-ethylcarbazole with tetrachlorosilane comparably led to a product with four 9-ethylcarbazol-3-yl units attached to silicon.³⁵⁰ Given a choice between a 3-bromo and an 8-chloro group, butyllithium exchanges bromine rather than chlorine.³⁵⁰

3-Bromo-1-methoxycarbazole was transformed into 1-methoxy-3-formylcarbazole by reaction with butyllithium and then with *N*-methylformanilide.⁴⁶⁶ 3-Bromo-9-isobutylcarbazole was transformed into the 3-aldehyde and the 3-vinyl analogs by successive treatments with butyllithium and dimethylformamide and acetaldehyde followed by potassium hydroxide, respectively.⁶³

⁴⁶¹ K. Saito and Y. Kikugawa, *J. Heterocycl. Chem.* **16**, 1325 (1979).

⁴⁶² R. O. Matevosyan, G. N. Yashchenko, A. K. Chirkov, and L. A. Perelyaeva, *Zh. Org. Khim.* **41**, 1670 (1968) [*CA* **70**, 3727y (1969)].

⁴⁶³ A. N. Novikov, L. F. Kovaleva, V. P. Lopatinskii, and L. P. Borodulina, *Zh. Org. Khim.*, 665 (1977) [*CA* **87**, 5755f (1977)].

⁴⁶⁴ Asahi Glass Co. Ltd., Jpn. Kokai Tokyo Koho 81/32,458 [*CA* **95**, P115289e (1981)].

⁴⁶⁵ A. Gilman and J. W. Diehl, *J. Org. Chem.* **26**, 2938 (1961).

⁴⁶⁶ J. D. Crum and P. W. Sprague, *Chem. Commun.*, 417 (1966).

7. Oxygen

Methylation of carbazole phenolic oxygen has been achieved using dimethyl sulfate without reaction at nitrogen.³⁵⁵ Demethylation of carbazole methyl ethers has been achieved with hydrobromic acid–acetic acid,^{302,467} boron trichloride,^{405,406} and pyridine hydrochloride.³⁰⁶ Selective demethylation of methoxyl ortho to an aldehydo function has been achieved using boron trifluoride.^{405,406} Partial demethylation of 1-methoxy-3-formylcarbazole occurred during Wolff–Kischner reduction.⁴⁰³

8. Silicon

The carbazole–silicon bond is hydrolyzed by hydrochloric acid–acetic acid; surprisingly, silicon at C-1 is cleaved by aqueous potassium hydroxide in hot ethanol, whereas silicon at C-3 is not.³⁵⁰

III. Synthesis of Carbazoles

The method that has been most utilized for the preparation of aromatic carbazoles from noncarbazole precursors is the dehydrogenation of a tricyclic indole, usually a 1,2,3,4-tetrahydrocarbazole. The synthesis of the latter^{467a,467b} is outside the scope of this article. The next most used precursors are biphenyls with an ortho nitrogen substituent, and the next, diphenylamines; the synthesis of these precursors is also not dealt with in detail here. Finally, a variety of approaches utilizing precursor indoles have been described; some of these have been used only once, whereas others have been used often enough that they can be described as general.

A. BY DEHYDROGENATION

A large number of carbazole syntheses have involved the preparation and dehydrogenation of hydrocarbazoles, mainly 1,2,3,4-tetrahydrocarbazoles, which are 2,3-disubstituted indoles. These, in turn, are usually prepared by the Fischer indole synthesis^{467a} or the Bischler synthesis.^{467b} This section will not deal with the preparation of the tetrahydrocarbazole, because

⁴⁶⁷ A. H. Milne and M. L. Tomlinson, *J. Chem. Soc.*, 2789 (1952).

^{467a} B. Robinson, "The Fischer Indole Synthesis." Wiley (Interscience), New York, (1982).

^{467b} R. K. Brown, in *Chem. Heterocycl. Compd.* **25**, Part I, 317 (1972).

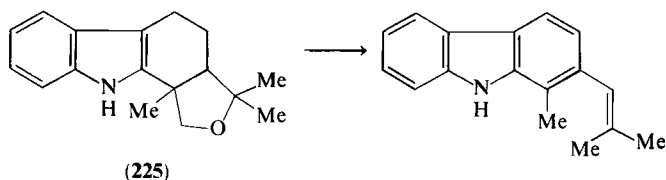
this is really indole chemistry, but will simply survey methods used for dehydrogenation. Two methods have been used far more than any others for the dehydrogenation of 1,2,3,4-tetrahydrocarbazoles: heating with palladium/charcoal^{163,186,341,351,353,354,356,403,434,435,438,460,467-484,490} and heating with chloranil in a solvent.^{192,318,341,404,439,460,466,469,471,472,485-490}

1. Metal Catalysis

In the noble metal catalysis process temperatures of about 200–350°C are generally used, often without a solvent, although sometimes xylene or *p*-cymene have been employed. Palladium is the

- ⁴⁶⁸ T. Masamune, G. Homma, and M. Ohno, *J. Fac. Sci., Hokkaido Univ., Ser. 3* **5**, 59 (1957) [CA 52, 10998d (1958)].
- ⁴⁶⁹ W. E. Noland and S. R. Wann, *J. Org. Chem.* **44**, 4402 (1979).
- ⁴⁷⁰ R. Fusco, and F. Sannicolo, *Tetrahedron Lett.*, 4827 (1978).
- ⁴⁷¹ H. Biere, H. Ahrens, C. Rufer, E. Schroeder, and H. Koch, German Patent 2,431,292 [CA 84, 164603j (1976)].
- ⁴⁷² H. Biere, H. Ahrens, C. Rufer, and E. Schroeder, German Patent 2,337,154 [CA 82, P156068g (1975)].
- ⁴⁷³ K. D. Berlin, P. E. Clark, J. T. Schroeder, and D. G. Hopper, *Proc. Okla. Acad. Sci.* **47**, 215 (1968) [CA 70, 96537z (1969)].
- ⁴⁷⁴ E. E. Campaigne and R. D. Lake, *J. Org. Chem.* **24**, 478 (1959).
- ⁴⁷⁵ G. Smolinsky, *J. Am. Chem. Soc.* **83**, 2489 (1961).
- ⁴⁷⁶ D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya, and A. K. Biswas, *Phytochemistry* **17**, 834 (1978).
- ⁴⁷⁷ M. Julia and J. Lenzi, *Bull. Soc. Chim. Fr.*, 2262 (1962).
- ⁴⁷⁸ T. D. Petrova, V. P. Mamaev, and G. G. Yakobson, *Izv. Akad. Nauk SSSR Ser. Khim.*, 679 (1969) [CA 71, 30318t (1969)].
- ⁴⁷⁹ A. C. Geale, J. M. G. Linnell, and M. L. Tomlinson, *J. Chem. Soc.*, 1124 (1956).
- ⁴⁸⁰ K. S. Murthy, R. Srinivasan, and K. Venkataraman, *J. Sci. Ind. Res., Sect. B* **21**, 290 (1962) [CA 57, 9782d (1962)].
- ⁴⁸¹ D. P. Chakraborty and E. K. Chowdhury, *Sci. Cult.* **32**, 590 (1966) [CA 67, 53975m (1967)].
- ⁴⁸² V. I. Shvedov, L. B. Altukhova, E. K. Komissarova, and A. N. Grinev, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSSR*, 365 (1965) [CA 63, 14800f (1965)].
- ⁴⁸³ L. G. Rashidyan, S. N. Asratyan, K. S. Karagezyan, A. R. Mkrtchyan, R. O. Sedrakyan, and G. T. Tatevosyan, *Arm. Khim. Zh.* **21**, 793 (1968). [CA 71, 21972z (1969)]
- ⁴⁸⁴ R. E. Moore and H. Rapoport, *J. Org. Chem.* **32**, 3335 (1967).
- ⁴⁸⁵ D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *Chem. Ind. (London)*, 1684 (1966).
- ⁴⁸⁶ R. B. Carlin and M. S. Moores, *J. Am. Chem. Soc.* **84**, 4107 (1962).
- ⁴⁸⁷ B. Miller and E. R. Matjeka, *J. Am. Chem. Soc.* **102**, 4772 (1980).
- ⁴⁸⁸ E. J. Forbes, M. Stacey, J. C. Tatlow, and R. T. Wragg, *Tetrahedron* **8**, 67, 79 (1960).
- ⁴⁸⁹ J. C. Blazejewski and C. Wakselman, *J. C. S. Perkin I*, 2845 (1980).
- ⁴⁹⁰ R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 976 (1952).

metal most used. Groups that survive these conditions include the following groups: alkyl,^{63,186,341,435,469-474,490} trifluoroalkyl,^{471,472} alkoxy,^{435,467,471,472,474,484} alkoxycarbonyl,^{351,354,438,469,471,476,477} cyano,^{351,354,356} halogeno^{471,472} (although 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydrocarbazole gave carbazole itself⁴⁷⁸ and 8-bromo-1,2,3,4-tetrahydrocarbazole lost its halogen¹⁹²), aryl,^{474,479} carbazol-9-yl,⁴⁷⁹ and acetamido.⁴⁸⁰ Carbonyl groups at the 1- and 4-positions of the tetrahydro ring have been shown to end up as phenolic hydroxyl groups.^{403,460,481,482} Loss of both carboxyl groups occurred on attempted dehydrogenation of 1,2,3,4-tetrahydrocarbazol-3,4-dicarboxylic acid; the difficulty was surmounted by conversion to the benzylamine imide, dehydrogenation, and hydrolysis.⁴⁸³ Dehydrogenation of 3,4-dihydro-2-formyl-1-methylcarbazole in *p*-cymene gave some 2,3-dimethylcarbazole but mainly the required carbazole aldehyde in benzene solution.³⁵³ Dehydrogenation of ether **225** gave 1-methyl-2-isobutenylcarbazole.³⁵³



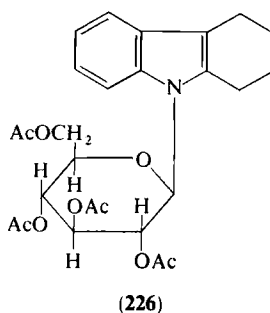
Palladium-charcoal has also been used in the presence of cinnamic acid as a hydrogen acceptor.⁴³⁴ Raney nickel alone and in the presence of hydrogen acceptors, the best being cyclohexanone, has also been utilized, although dehydrogenation did not occur with 6-chloro- and 6-nitro-1,2,3,4-tetrahydrocarbazoles.⁴⁹¹ Selenium has also been used.⁴⁶⁸

2. Quinone Oxidation

Chloranil is also widely applicable for the dehydrogenation of 1,2,3,4-tetrahydrocarbazoles; it is generally employed in xylene solution. Substituents that have survived this procedure include the following groups: alkyl,^{192,341,404,469,471,472,485-487,490} trifluoroalkyl,^{471,472,488} alkoxy,^{318,460,466,471,472,485} alkoxycarbonyl,^{404,469,471,472} halogeno,^{192,460,466,471,472} including fluorine,⁴⁸⁹ and nitro.⁴³⁹ 8-Bromo-

⁴⁹¹ W. E. Babcock and K. H. Pausaker, *J. Chem. Soc.*, 1373 (1951).

6-nitro-1,2,3,4-tetrahydrocarbazole could not be dehydrogenated with chloranil.¹⁹² As with metal-catalyzed dehydrogenation, 1-oxo- and 4-oxo-1,2,3,4-tetrahydrocarbazoles produce 1- and 4-hydroxycarbazoles, respectively.⁴⁶⁰ 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone was used to dehydrogenate *N*-glycosides such as **226**⁴⁹² and to transform 1,2,3,4-tetrahydro-1-hydroxy-8-hydroxymethylcarbazole into 1-formyl-8-hydroxycarbazole.^{492a} *p*-Benzoquinone itself dehydrogenates 1,2,3,4-tetrahydrocarbazole, 1,4-dihydrocarbazole, and 6-bromo-1,2,3,4-tetrahydrocarbazole.⁴⁹³



3. Other Chemical Oxidations

Other chemical reagents that have been used to dehydrogenate are diphenyl disulfide⁴⁹⁴ for 1,2,3,4-tetrahydrocarbazole itself, *N*-bromosuccinimide in pyridine for 1-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole,⁴⁹⁵ selenium dioxide for 9-methyl-1,2,3,4-tetrahydrocarbazole (a 1:5 mixture of 9-methylcarbazole and 1-oxo-1,2,3,4-tetrahydrocarbazole was obtained⁴⁹⁶), and manganese dioxide to aromatize 1-methyl- and 1,4-dimethyl-6-alkoxy-3-formyl-1,2,3,4-tetrahydrocarbazoles³⁵⁹ and 1,9-diprenyl-1,4-dihydrocarbazole.¹⁹

⁴⁹² V. S. Martynov, T. Ya. Filipenko, and M. N. Preobrazhenskaya, *Zh. Org. Khim.* **10**, 1117 (1974) [*CA* **81**, 63916w (1974)].

^{492a} S. Majumdar and L. Bhattacharya, *J. Indian Chem. Soc.* **58**, 91 (1981).

⁴⁹³ G. Manecke, G. Kossmehl, R. Gawlik, and G. Hartwich, *Angew. Makromol. Chem.* **6**, 89 (1969) [*CA* **71**, 3950m (1969)].

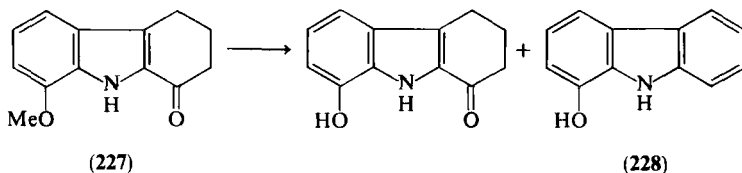
⁴⁹⁴ M. Nakasaki, *J. Chem. Soc. Jpn., Pure Chem. Sect.* **74**, 403 (1953) [*CA* **48**, 12017i (1954)].

⁴⁹⁵ R. J. Owellen and C. A. Hartke, *J. Org. Chem.* **41**, 102 (1976).

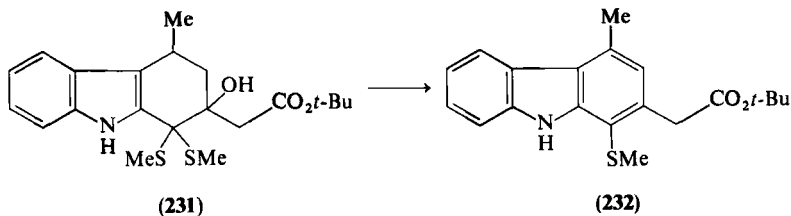
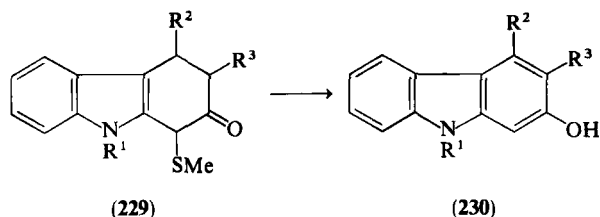
⁴⁹⁶ S. Sakai, A. Kubo, K. Katsuura, K. Mochinaga, and M. Ezaki, *Chem. Pharm. Bull.* **20**, 76 (1972).

4. Miscellaneous

Pyridine hydrochloride caused an interesting effective loss of water from various Ar-alkyl- and Ar-alkoxyl-substituted 1-oxo-1,2,3,4-tetrahydrocarbazoles (available via the Japp-Klingemann 2-acylindole synthesis^{496a}) and formation of the corresponding carbazoles, with demethylation of phenolic methoxyl groups also occurring. For example, **227** gave the carbazole **228** along with the demethylated ketone after a short time and the hydroxycarbazole only after a longer time.⁴⁹⁷



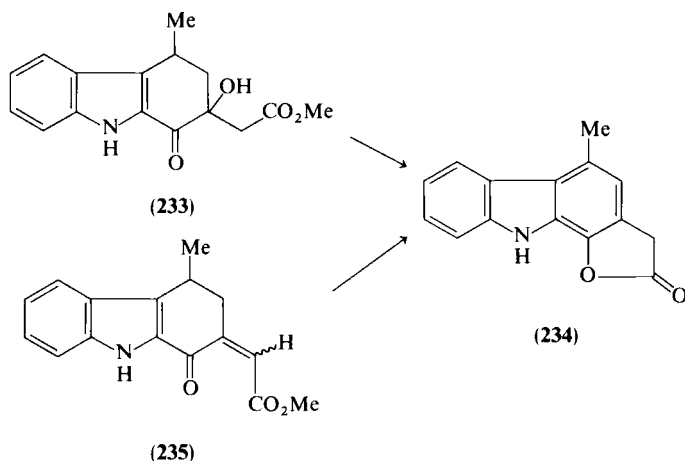
The thioether ketones **229** ($R^1 = R^2 = R^3 = H$; $R^1 = Me$, $R^2 = R^3 = H$; $R^1 = PhCH_2$, $R^2 = R^3 = H$; $R^1 = Me$, $R^2 = H$, $R^3 = NHAc$) lost the thiol and produced the corresponding 2-hydroxycarbazoles (**230**) on treatment with *p*-toluenesulfonic acid in acetonitrile.⁴⁹⁸ Similarly the thioacetal **231** lost 1-mol equivalent of thiol and one of water, giving carbazole **232** in acetic acid. Ketone **233** gave the lactone **234** on dehydration with *p*-toluenesul-



^{496a} R. R. Phillips, *Org. React.* **10**, 143 (1959).

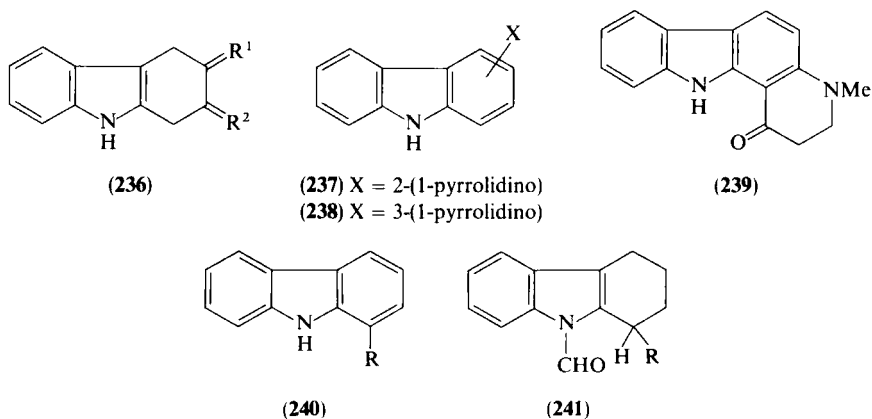
⁴⁹⁷ E. Bisagni, C. Ducrocq, and Nguyen Chi Hung, *Tetrahedron* **36**, 1327 (1980).

⁴⁹⁸ Y. Oikawa and O. Yonemitsu, *J. Org. Chem.* **41**, 1118 (1976).



fonic acid in xylene; the same lactone resulted from comparable treatment of **235**.³⁵⁵

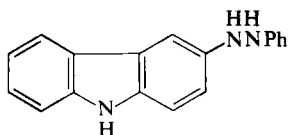
Exposure of the ketones **236** ($R^1 = H_2$, $R^2 = 0$ and $R^1 = 0$, $R^2 = H_2$) to typical enamine-forming conditions gave the aromatized pyrrolidinocarbazoles **237** and **238**, respectively, by aerial oxidation during work-up.⁴⁹⁹ Treatment of **236** ($R^1 = H_2$, $R^2 = 0$) with 3-methylaminopropanoic acid gave **239**.⁴⁹⁹ Some 1-substituted carbazole **240** as well as the hydrogenolyzed 1,2,3,4-tetrahydrocarbazole **241** were formed on Fischer formic acid cyclization of the phenylhydrazone of 2-hydroxy-2-alkylcyclohexanones.⁵⁰⁰



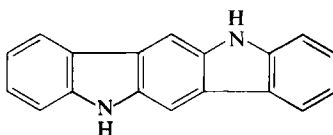
⁴⁹⁹ Y. Kumar, A. K. Saxena, P. C. Jain, and N. Anand, *Indian J. Chem. Sect. B*, **19B**, 996 (1980).

⁵⁰⁰ T. Wakamatsu, H. Hara, and Y. Ban, *Heterocycles*, **8**, 335 (1977).

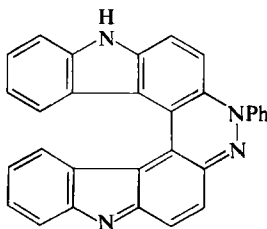
The Fischer sequence applied to the bisphenylhydrazone of cyclohexane-1,4-dione by warming in acetic acid-sulfuric acid gave the 3-phenylhydrazinocarbazole **242** as well as the indolocarbazole **243**.⁵⁰¹ In alcoholic sulfuric acid, 3-hydroxycarbazole, 3-aminocarbazole, and the pentacycle **243** were formed⁵⁰² along the helicene **244**.⁴⁴⁵



(242)

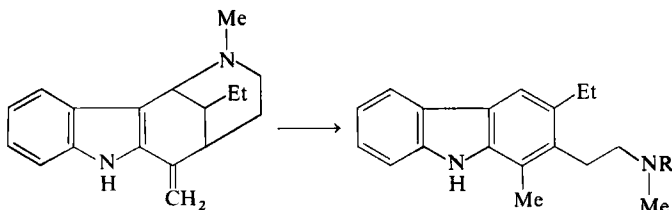


(243)



(244)

The alkaloid uleine **245** reacted with acetyl chloride-potassium carbonate,⁵⁰³ and its methiodide with aqueous base,⁵⁰⁴ to form ring-opened products, the carbazoles **246** (R = Ac and R = Me, respectively).



(245)

(246)

Several 9-methyl-1,2,3,4-tetrahydrocarbazoles gave the corresponding 1-methyl-3-formylcarbazoles when subjected to Vilsmeier conditions. The process is believed to be initiated by C-1 formylation; it was demonstrated that the benzene ring carrying the two new C-1 units was the original tetrahydro ring.⁴⁰⁹

⁵⁰¹ B. Robinson, *J. Chem. Soc.*, 3097 (1963).

⁵⁰² H. J. Teuber and L. Vogel, *Chem. Ber.* **103**, 3302 (1970).

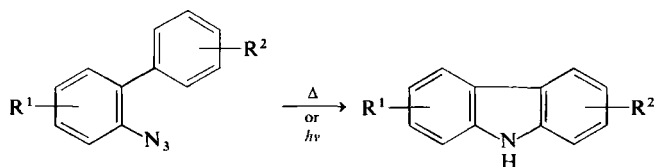
⁵⁰³ J. A. Joule and C. Djerassi, *J. Chem. Soc.*, 2777 (1964).

⁵⁰⁴ J. Schmutz, F. Hunziker, and R. Hirt, *Helv. Chim. Acta* **41**, 288 (1958).

B. FROM BIPHENYLS

1. *o*-Azidobiphenyls

An important route to the carbazole ring system involves the thermal^{192,454,475,484,505-511} or photochemical^{221,453,506,511-519} decomposition of *o*-azidobiphenyls prepared from the *o*-aminobiphenyls via the diazonium salt. Nitrogen is evolved and a nitrene is produced that effectively inserts into the ortho C—H bond of the second ring.⁵⁰⁹



The thermal process has been conducted in hot kerosene,^{192,506,507} in *n*-hexadecane,⁴⁷⁵ in *o*-dichlorobenzene,⁵⁰⁸ in di-*n*-hexyl ether,⁴⁸⁴ and in chlorobenzene.⁵¹⁰ Tetrachlorothiophene has been recommended for similar processes.⁵²⁰ A low concentration is advantages (<1% was recommended in work that showed kerosene to be the optimal solvent.⁵⁰⁶) As high a temperature as possible has been recommended.^{520,521} The process has been conducted with alkyl,⁴⁸⁴ nitro,^{192,506,508} bromo,^{192,506} methoxyl,^{475,484,507,509} hydroxyl,⁵⁰⁹ and even (additional) azido⁴⁵⁴ groups

⁵⁰⁵ P. A. S. Smith and J. H. Hall, *J. Am. Chem. Soc.* **84**, 480 (1962).

⁵⁰⁶ P. A. S. Smith and B. B. Brow, *J. Am. Chem. Soc.* **73**, 2435 (1951).

⁵⁰⁷ C. K. Bradsher, F. C. Brown, and P. H. Leake, *J. Org. Chem.* **22**, 500 (1957).

⁵⁰⁸ B. D. Mendenhall and P. A. S. Smith, *Org. Synth.* **46**, 85 (1966).

⁵⁰⁹ P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.* **23**, 524 (1958).

⁵¹⁰ H. W. Moore, W. Weyler, and H. R. Sheldon, *Tetrahedron Lett.*, 3947 (1969).

⁵¹¹ J. Sauer and J. Engels, *Tetrahedron Lett.*, 5175 (1969).

⁵¹² J. S. Swenton, *Tetrahedron Lett.*, 3421 (1968).

⁵¹³ J. S. Swenton, T. J. Ikeler, and B. W. Williams, *Chem. Commun.*, 1263 (1969).

⁵¹⁴ A. Reiser, H. Wagner, and G. Bowes, *Tetrahedron Lett.*, 2635 (1966); *Trans. Faraday Soc.* **64**, 3265 (1968).

⁵¹⁵ P. A. Lehman and B. R. Stephen, *J. Am. Chem. Soc.* **95**, 8614 (1973).

⁵¹⁶ R. J. Sundberg, D. W. Gillespie, and B. A. De Graff, *J. Am. Chem. Soc.* **97**, 6193 (1975).

⁵¹⁷ R. J. Sundberg and R. W. Heintzelman, *J. Org. Chem.* **39**, 2546 (1974).

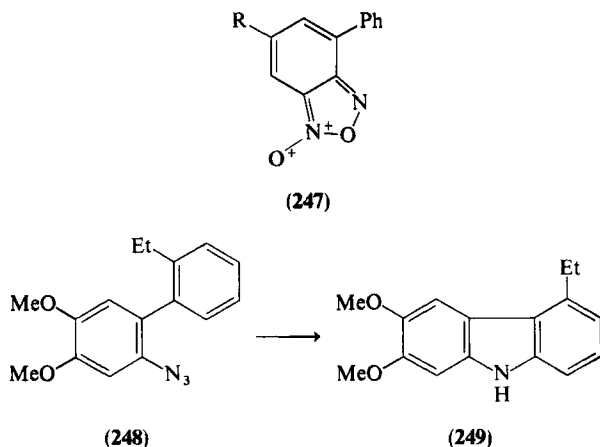
⁵¹⁸ A. Yabe, *Bull. Chem. Soc. Jpn.* **53**, 2933 (1980).

⁵¹⁹ J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Am. Chem. Soc.* **92**, 3103 (1970).

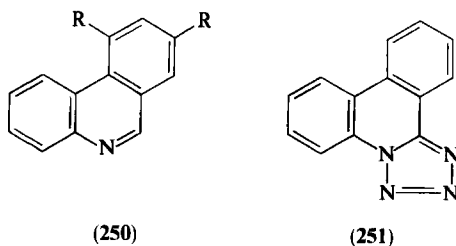
⁵²⁰ J. M. Lindley, I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 2194 (1977).

⁵²¹ J. M. Lindley, I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Lett.*, 4513 (1976).

present. However, 3-mono- and 3,6-dinitro-2-azidobiphenyls gave **247** ($R = H$ and NO_2).⁵⁰⁶ 2'-Substituted 2-azidobiphenyls gave 4-substituted carbazoles,^{475,484,509} not easily available by substitution processes, although 2'-nitro-2-azidobiphenyl did not give a carbazole.⁵⁰⁶ 4-Methoxy-⁴⁷⁵ and 4-aminocarbazole were prepared in this way.⁴⁵⁴ 4- or 4'-Substituted 2-azidobiphenyls gave 2-substituted carbazoles,^{506,509} and 3- or 3'-substituted 2-azidobiphenyls gave 1-substituted carbazoles,^{506,509} the latter also not easily obtained by substitution of intact carbazoles. 2-Nitrocarbazole,^{506,508} 2-methoxycarbazole,^{507,509} 2-hydroxycarbazole,⁵⁰⁹ and 1,4-dimethoxycarbazole⁵⁰⁹ were thus prepared. The azide **248** was resistant to heat alone but addition of palladium-charcoal brought about the desired conversion to **249**.⁴⁸⁴



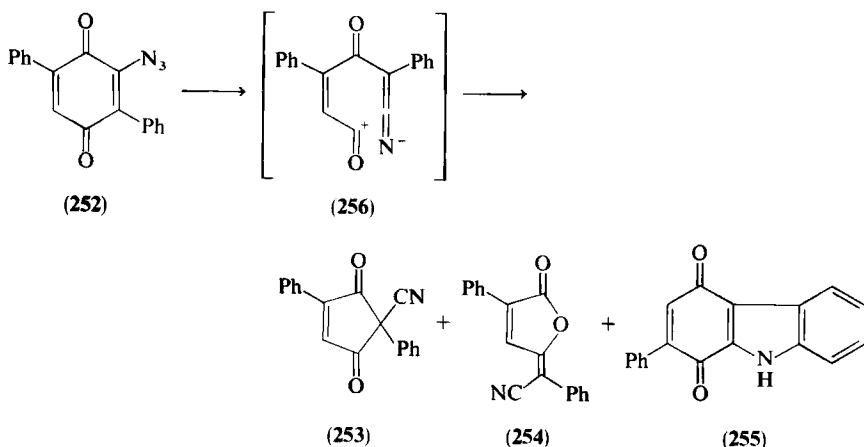
2',4,6'-Trimethyl-2-azidobiphenyl thermolyzed in *n*-hexadecane gave only 4% 2,4,9-trimethylcarbazole, that is, the product of nitrene insertion into the ortho C-methyl bond; the main products were 2'-amino-2,4,6-trimethylbiphenyl and **250** ($R = Me$).⁵²² An intramolecular dipolar cycloaddition com-



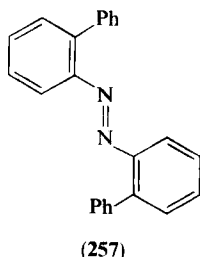
⁵²² G. Smolinsky, *J. Am. Chem. Soc.* **82**, 4717 (1960).

peted effectively with azide decomposition when 2'-cyano-1-azidobiphenyl was heated in kerosene resulting in the formation of the tetrazole **251**.⁵²³

The diphenyl *p*-benzoquinone azide **252** heated in chlorobenzene gave mainly **253**, traces of **254**, and 20% of the carbazole quinone **255**.⁵¹⁰ Initial fragmentation with loss of nitrogen to **256**, collapse of which could lead to **253** and **254**, is the rationalization presented; formation of the carbazole is viewed as the usual nitrene insertion.⁵¹⁰



The simple photochemical transformation⁵⁰⁶ of *o*-azidobiphenyls into carbazoles is preparatively useful. Considerable effort has been expended on study^{512-517, 519, 520, 524} of the mechanism of this process. Both carbazole and dimerized nitrene, for example **257**, can be produced in the process: in



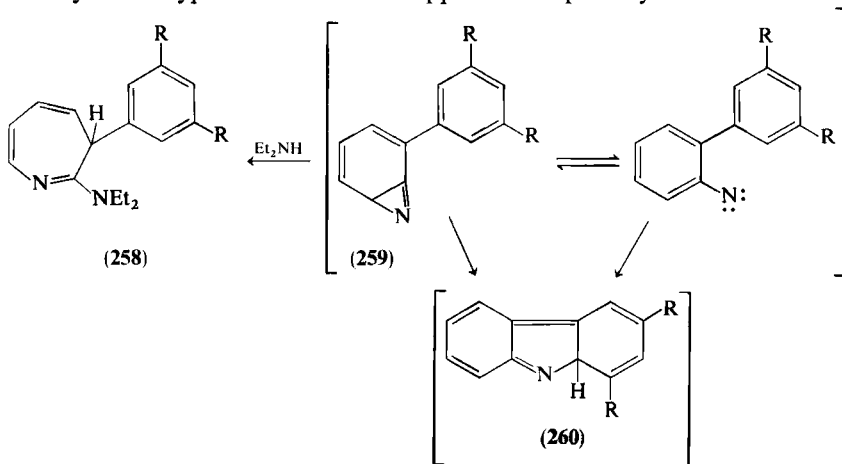
acetone solution 28% and 41%, respectively, in the unsubstituted series.⁵¹² Irradiation without sensitizers gives mainly the carbazole.⁵¹⁹ In benzene solution with ketone sensitizers, mainly dimer is produced^{512, 513, 519}; in ether, benzene, or isopropanol mainly carbazole is produced⁵¹³; and in ether or

⁵²³ P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.* **23**, 524 (1958).

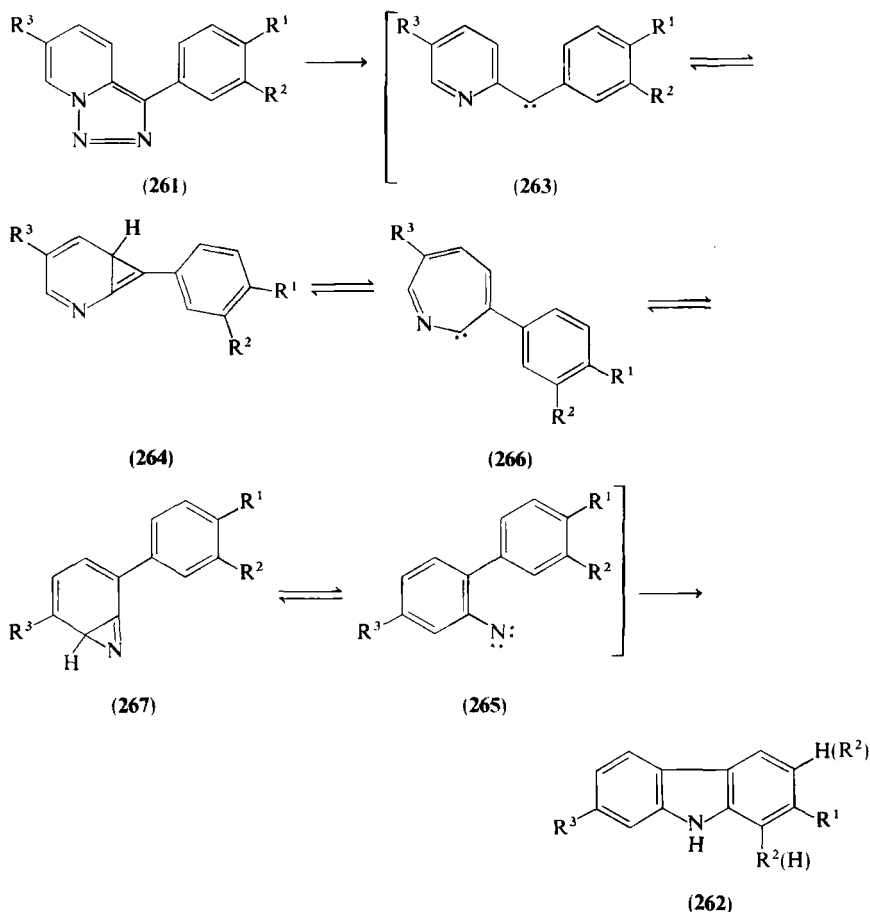
⁵²⁴ P. A. Lehmann and R. S. Berry, *J. Am. Chem. Soc.* **95**, 8614 (1973).

benzene with sensitizers such as pyrene or naphthalene, only carbazole is produced.^{512,513,519} As high a temperature as possible aids carbazole formation in the photochemical process.⁵²¹

Working in EPA at 77 K, an intermediate believed to be the triplet⁵¹⁵ nitrene was observed by UV spectroscopy.⁵¹⁴ Flash-photolysis techniques also recognized this same intermediate.⁵¹⁵⁻⁵¹⁷ Carbazole formation was at one time thought to involve a triplet^{512,524} nitrene as the key cyclizing intermediate; other workers preferred a singlet.^{513,516,517,519,520} Furthermore, the singlet nitrene may not be the only major carbazole precursor.^{516,517} For example, in irradiation of 3',5'-dimethyl-, 3',5'-trifluoromethyl-, and 3',5'-methoxycarbonyl-substituted biphenyl azides in the presence of diethylamine, azepines **258** were formed in addition to carbazoles. The proportion of azepine produced was greater with the electron-withdrawing groups present.⁵¹⁷ The nitrene may be in rapid equilibrium with an azirine **259**, which can be trapped by the secondary amine to give observed products **258**. Both nitrene and **259** can produce **260**, a non-trappable precursor of the carbazole.^{516,517} Such an intermediate may be the species observed spectroscopically in the low-temperature and flash-photolysis studies, rather than the nitrene itself. It is significant that in work on the thermolysis (500–900°C) of triazolopyridines **261**, which surprisingly gave carbazoles **262** ($R^1 = R^2 = R^3 = H$; $R^1 = OMe, Cl, NO_2, CN$, $R^2 = R^3 = H$; $R^1 = R^2 = H$, $R^3 = NO_2, OMe$; $R^1 = R^2 = H$, $R^3 = Me$) in high yields and in a state of high purity, the mechanism postulated is formation of carbene **263**, which inserts into the pyridine 2,3-bond to produce **264**, followed by formation of nitrene **265** via **266** and/or **267**,⁵²⁵ the latter being exactly of the type believed to be trapped in the photolytic work.⁵¹⁷

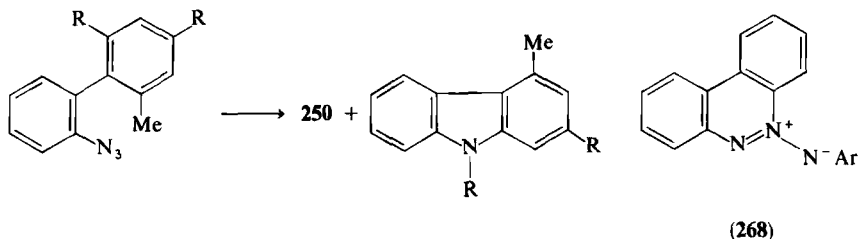


⁵²⁵ C. Mayor and C. Wentrup, *J. Am. Chem. Soc.* **97**, 7467 (1975).



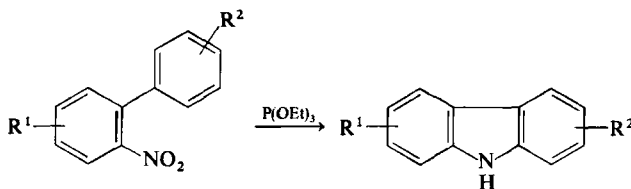
Although some 4-methylcarbazole was formed from photolysis of 2'-methyl-2-azidobiphenyl, the main product (**250**; $R = H$) was that resulting from nitrene insertion into a methyl C—H bond. With both *o'*-positions blocked by methyl groups, the main product was again **250** ($R = Me$), with a small amount of 2,4,9-trimethylcarbazole resulting from insertion into the C—Me bond.⁵¹⁸ The photolytic decomposition of 2'-aryazo-2-azidobiphenyl comparably produced some (10–15%) 4-arylazocarbazole, but the main products were the benzo[*c*]cinnoline *N*-arylimides **268**.⁴⁵³ Thermolysis gave somewhat lower amounts of carbazoles along with benzo[*c*]cinnoline itself.⁴⁵³ Finally, 2'-azido-2-azidobiphenyl photolyzed giving exclusively benzo[*c*]cinnoline at 77 K, but giving exclusively nitrene dimer when sensitized with benzophenone and up to 55% 4-azidocarbazole in heptane.^{454,526}

⁵²⁶ A. Yabe, and K. Honda, *Bull. Chem. Soc. Jpn.* **49**, 2495 (1976).



2. *o*-Nitrobiphenyls: The Cadogan Synthesis

The deoxygenation⁵²⁷ of *o*-nitrobiphenyls followed by the insertion of nitrene into the *o*'-carbon-hydrogen bond is a useful and versatile method for the synthesis of carbazoles.^{103,302,306,341,400,401,406,511,528-531} Refluxing triethyl phosphite is the usual reagent, triethyl phosphate being the by-product.



Of other reagents that have been similarly employed, tris(trimethylsilyl) phosphate has been recommended. The reaction was said to proceed faster and at lower temperature; the phosphoric acid by-product and unchanged reagent (after hydrolysis) are easily removed, being water soluble.⁵³² In a study of the use of disilanes, the best was **269**, although in general they do not seem to offer any advantages as deoxygenation agents.⁵³³ Benzyl alcohol in the presence of copper-alumina catalysts requires 360°C for reaction⁵³⁴; Raney nickel was used with 2,2'- and 2,3'-dinitrobiphenyls, and mixtures of benzo[*c*]cinoline and carbazole and 1-aminocarbazole, respectively were

⁵²⁷ J. I. G. Cadogan, *Synthesis* **1**, 11 (1969).

⁵²⁸ J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc. London*, 361 (1962); J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965).

⁵²⁹ G. W. Gray and D. Lewis, *J. Chem. Soc.*, 3501 (1964).

⁵³⁰ I. Puskas and E. K. Fields, *J. Org. Chem.* **33**, 4237 (1968).

⁵³¹ D. E. Ames, K. J. Hansen, and N. D. Griffiths, *J. C. S. Perkin I*, 2818 (1973).

⁵³² M. Sekine, H. Yamagata, and T. Hata, *Tetrahedron Lett.*, 375 (1979).

⁵³³ F.-P. Tsui, T. M. Vogel, and G. Zon, *J. Org. Chem.* **40**, 761 (1975).

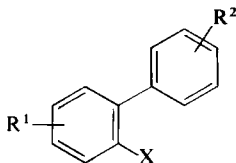
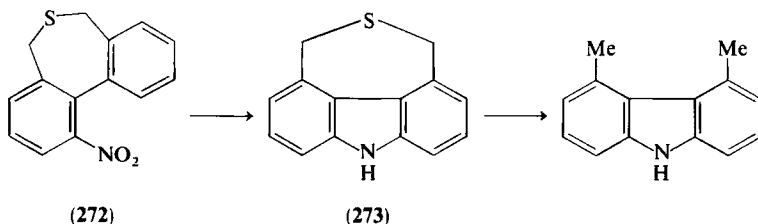
⁵³⁴ N. S. Kozlov, B. I. Kiselev, and T. A. Skorokhodova, *Dokl. Akad. Nauk BSSR* **14**, 536 (1970) [*CA* **73**, 87720p (1970)].

produced.⁵³⁵ A nitrenium cation was suggested as an intermediate in the ferrous oxalate conversion of 2-nitrobiphenyl to carbazoles.⁵³⁶ In the ferrous oxalate reduction of 2-cyclohexylnitrobenzene, 40% of carbazole was produced along with *o*-aminophenylcyclohexane.⁵³⁷



(269)

The triethyl phosphite deoxygenation process tolerates aromatic bromine,⁵²⁸ methoxyl,^{302,306,406} phenyl,⁵²⁹ and alkyl,^{103,302,306,401,528,531} including *tert*-butyl,^{400,401} substituents. Occasionally 9-ethylcarbazoles have resulted from more prolonged treatments with triethylphosphite.^{400,530} The 9-alkylation is caused not by triethyl phosphite but by nitrene side products **270** and **271**.¹⁰³ A low yield of 4,5-dimethylcarbazole attributed to an unfavorable steric interaction in the nitrene intermediate was nicely overcome by using thioether **272**, desulfurization of the tetracyclic carbazole **273** giving the target dimethylcarbazole.⁵³¹ Among the carbazoles that have been efficiently prepared using the Cadogan synthesis are 4-methyl-^{400,528}; 4-bromo-⁵²⁸; 2-methyl-⁵²⁸; 2-bromo-⁵²⁸; 2-phenyl-⁵²⁹; tetra-, penta- hexa-methyl-⁵³⁰; and 2- and 2,7-di-*tert*-butylcarbazoles.⁴⁰¹

(270) X = N=P(OEt)₃(271) X = NHPO(OEt)₂

(272)

(273)

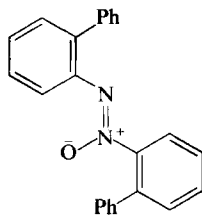
⁵³⁵ I. Puskas, E. K. Fields and E. M. Banas, *Prepr., Div. Pet. Chem., Am. Chem. Soc.* **17**, B6 (1972) [CA **79**, 137068d (1973)].

⁵³⁶ Y. Yost, *J. Heterocycl. Chem.* **9**, 151 (1972).

⁵³⁷ R. A. Abramovitch, Y. Ahmad, and D. Newman, *Tetrahedron Lett.*, 752 (1961).

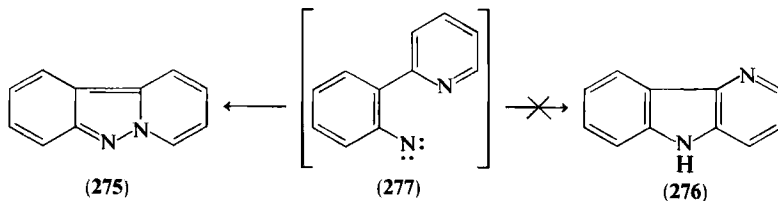
3. *o*-Nitrosobiphenyls

Triethyl phosphite will also efficiently convert 2-nitrosobiphenyl to carbazole⁵³⁸ at 0–5°C. Because of the relative ease of synthesis of aromatic nitro and nitroso compounds, this offers no synthetic advantage and no exploitations have been reported. 2-Nitrosobiphenyl also gave carbazole along with 2-aminobiphenyl and **274** by co-condensation with chromium atoms at 77 K.⁵³⁹ The conversion of 2-nitrobiphenyl to carbazole (21%) and 2-anilino-biphenyl with excess phenylmagnesium bromide is believed to proceed via 2-nitrosobiphenyl.⁵³⁶ Attempted deoxygenation of 2-nitrosobiphenyl with hexamethyldisilane gave only tars.⁵³³



(274)

The fact that the ratio (55:45) of 1-methylcarbazole to 3-methylcarbazole was effectively the same when obtained either via the triethylphosphite (or trisdimethylaminophosphine) deoxygenation of 2-nitro-3'-methylbiphenyl or of 2-nitroso-3'-methylbiphenyl or via the thermal or photochemical decomposition of the corresponding azides is taken as strong circumstantial evidence that each process proceeds via a common intermediate—the nitrene.⁵¹¹ The electrophilic nature of such a nitrene was well illustrated by the formation of **275** and not **276** from the nitrene **277**.^{537,538}



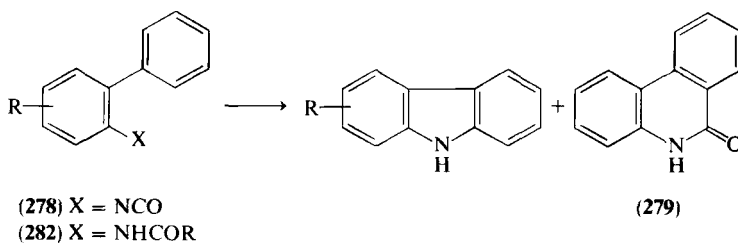
4. *o*-Isocyanatobiphenyls

The direct photolysis of *o*-isocyanatobiphenyls **278** is yet another means for the generation of nitrene, which leads via cyclization to a carbazole. How-

⁵³⁸ P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 42 (1963).

⁵³⁹ S. Togashi, J. G. Fulcher, B. R. Cho, M. Hasegawa, and J. A. Gladysz, *J. Org. Chem.* **45**, 3044 (1980)

ever, 6(5*H*)-phenanthridones **279** are also produced and are formed exclusively on sensitized irradiation.⁵⁴⁰

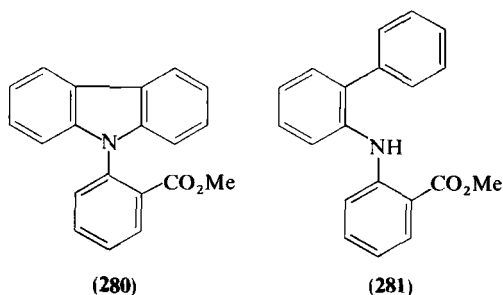


5. *o*-Hydroxylaminobiphenyls

Dissolving *o*-hydroxylaminobiphenyl in concentrated sulfuric acid gave the typical carbazole blue color; basification produced carbazole quantitatively.⁵³⁶ More dilute sulfuric acid and hydrofluoric acid were less efficient in forming the heterocycle, presumed to be produced via a nitrenium cation.⁵⁴¹

6. *o*-Aminobiphenyls

Vapor phase pyrolysis of 2-aminobiphenyl in chloroform at 350°C produces carbazole,⁵⁴² as does heating at 500–800°C in a high-frequency glow discharge at 25–34 W.⁵⁴³ A small amount (11%) of carbazole **280** was formed during the reaction of **281** with copper–potassium carbonate and 1-iodonaphthalene in nitrobenzene.¹³⁶



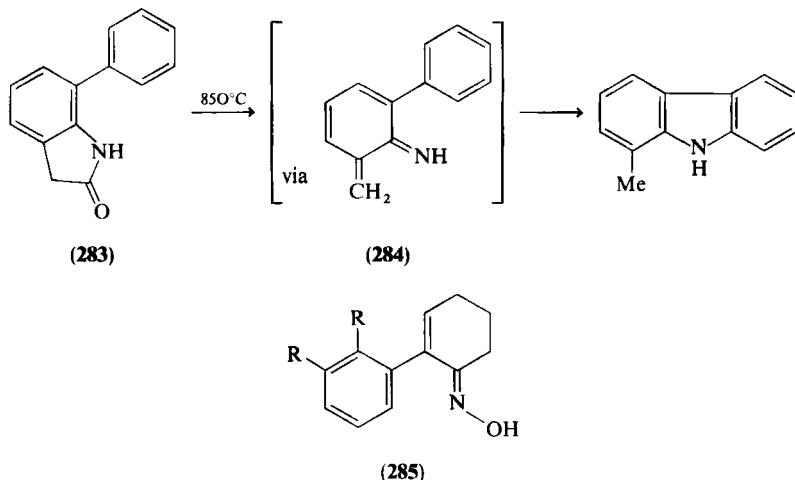
⁵⁴⁰ J. S. Swenton, T. J. Ikeler, and G. Le Roy Smyser, *J. Org. Chem.* **38**, 1157 (1973).

⁵⁴¹ T. B. Patrick and J. A. Schield, *Tetrahedron Lett.*, 445 (1973).

⁵⁴² R. E. Burby, S. M. Hussain, M. Bin Mohamed, J. Parrick, C. J. G. Shaw, I. A. Bhatti, and A. H. Shirazi, *J. Chem. Res. Synop.*, 408; *J. Chem. Res., Miniprint*, 4935 (1980).

⁵⁴³ H. Suhr, U. Schoech, and G. Roskamp, *Chem. Ber.* **104**, 674 (1971).

Intramolecular displacement of halogen catalyzed by copper resulted in the efficient synthesis of 9-tosyl- and 9-mesylcarbazoles from the 2'-bromo-2-tosylamido- and 2'-bromo-2-mesylamidobiphenyls.¹⁹⁷ The extraordinary nonaromatic spiro salts **49** (R = H or Me) and the dibenz[4,5:6,7]azepino[1,2,3-*jk*]carbazoles **50** resulted from diazotization then heating of precursor amine¹³⁷ (compare with the transformation of **168** into **169**, Section II,D,2). Persulfate oxidation of *o*-amidobiphenyls (**282**; R = Me or Ph) gave the 9-acylcarbazoles in low yield.⁵⁴⁴ Heating 7-phenyloxindole (**283**) at 850°C produced 43% of 1-methylcarbazole and some carbazole,⁴⁰² perhaps via **284**.⁵⁴⁵ Carbazoles are also formed upon heating oximes (**285**; R = H and OMe).⁵⁴⁶



7. 2,2'-Diaminobiphenyls: The Taüber Synthesis

2,2'-Diaminobiphenyls give carbazoles in good yield when treated with hot, strong acid; phosphoric acid at 200°C has been most frequently used.^{341,547-549} Zinc chloride-hydrogen chloride⁵⁵⁰ and heating alone⁵⁵¹

⁵⁴⁴ P. M. Brown, P. S. Dewar, A. R. Forrester, A. S. Ingram, and R. H. Thomson, *Chem. Commun.*, 849 (1970).

⁵⁴⁵ C. Wentrup, *Adv. Heterocycl. Chem.* **28**, 256 (1981).

⁵⁴⁶ A. Löffler and D. Ginsburg, *Nature (London)* **172**, 820 (1953).

⁵⁴⁷ H. Leditschke, *Chem. Ber.* **86**, 522 (1953).

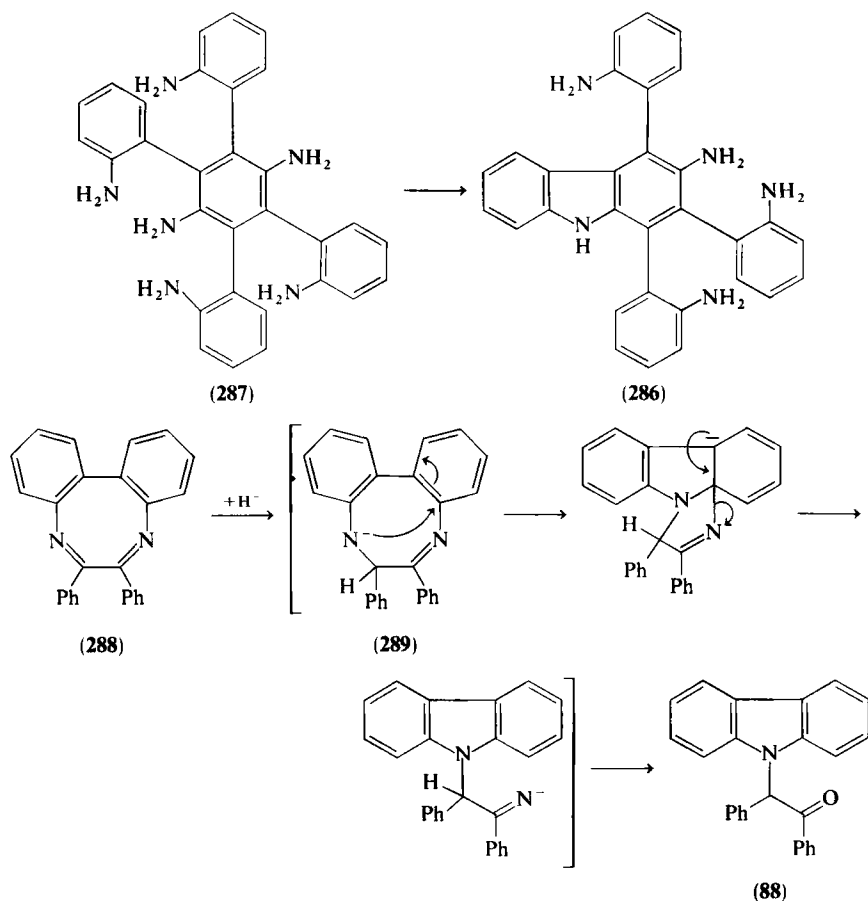
⁵⁴⁸ N. Tokura and S. Anazawa, *Sci. Rep. Res. Inst., Tohoku Univ., Ser. A* **9**, 239 (1957) [*CA* **52**, 1964f (1958)].

⁵⁴⁹ M. Tashiro, *Jpn. Kokai Tokyo Koho* 80/127,370 [*CA* **94**, P192135h (1981)].

⁵⁵⁰ W. Theilacker and F. Baxmann, *Justus Liebigs Ann. Chem.* **581**, 117 (1953).

⁵⁵¹ Z. J. Allan and F. Müzik, *Chem. Listy* **48**, 52 (1954).

have also been employed. Halogen,⁵⁴⁷ nitro,⁵⁴⁷ amino,^{550,551} aryl,⁵⁵¹ and alkyl^{341,550} substituents survive the relatively vigorous treatment, although *tert*-butyl groups were lost.⁵⁴⁹ The very heavily substituted carbazole **286** was apparently prepared by this route from **287** by heating at 170°C.⁵⁵¹ Another extraordinary reaction is the lithium aluminium hydride conversion of diimine **288** via **289** to carbazole ketone **88**; the sequence suggested to rationalize the transformation is shown.²²²

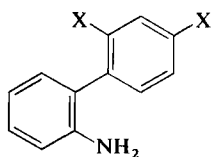


Benzo[*c*]cinnoline is reduced by visible-light photolysis in isopropanol to 5,6-dihydrobenzo[*c*]cinnoline; irradiation of this at a shorter wavelength converts it to carbazole.⁵⁵²

⁵⁵² H. Inoue, T. Sakurai, and F. Tanaka, *Bull. Chem. Soc. Jpn.* **48**, 924 (1975); H. Inoue, Y. Hiroshima, and K. Miyazaki, *ibid.*, **52**, 664 (1979).

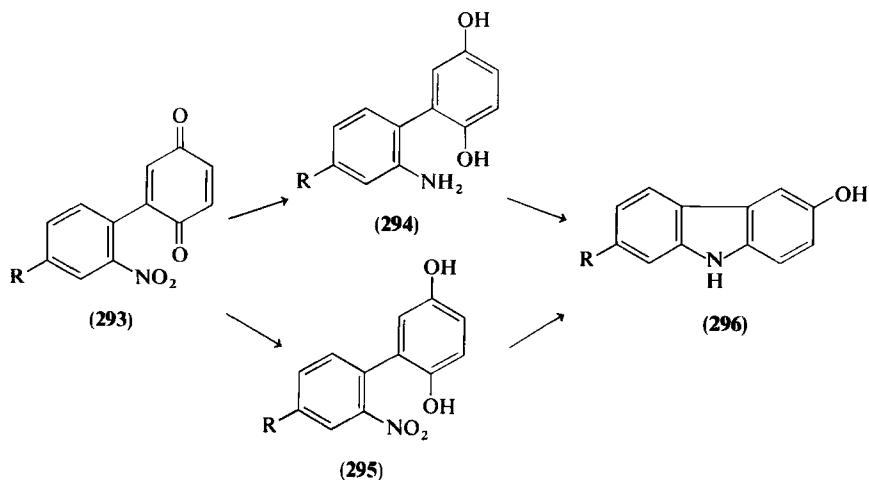
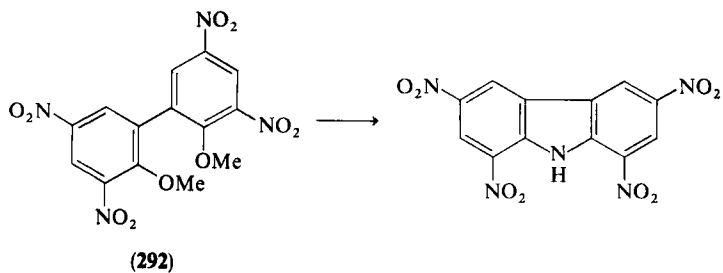
8. 2'-Oxy-2-aminobiphenyls

When the amino diether **290** was treated with pyridine hydrochloride, 2-hydroxycarbazole was formed; the probable intermediate **291**, formed from **290** with hydrogen bromide, was comparably transformed into 2-hydroxycarbazole with pyridine hydrochloride.⁵⁵³



(290) X = MeO

(291) X = OH

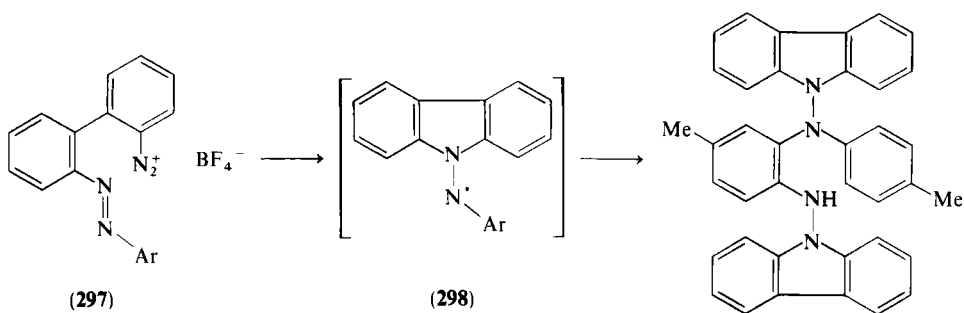


⁵⁵³ H. Erdtman, F. Haglid, and N. E. Stjernström, *Acta Chem. Scand.* **15**, 1761 (1961).

Presumably a 2'-oxy-2-aminobiphenyl is intermediate in the conversion of **292** with ammonia at 135°C to 1,3,6,8-tetranitrocarbazole.³⁶² The *p*-benzoquinones **293** (R = H, Me or OMe) gave **294** on reduction with hydrogen–palladium–acid and **295** on reduction with sulfur dioxide. Compound **294** on oxidation with iron(III) chloride and compound **295** on reduction with hydrogen–nickel produced the 3-hydroxycarbazoles **296**.⁵⁵⁴

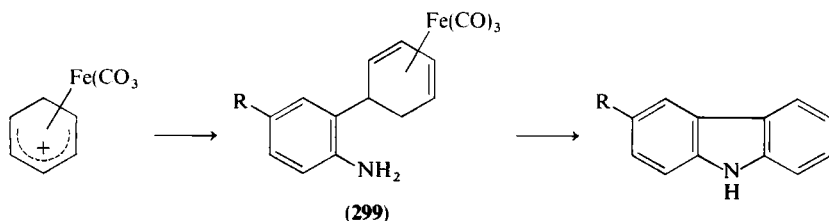
9. 2'-Arylazo-2-aminobiphenyls

The rarely encountered radical addition to N=N was observed in the decomposition of diazonium salts **297**. In some cases unstable derivatives of the initially formed radical **298** were obtained via nitrogen–nitrogen or nitrogen–*o*-carbon dimerization.²⁸⁵



10. 2-(*o*-Aminoaryl)cyclohexadiene Iron Tricarbonyls

The iodine oxidative closure of iron tricarbonyl complex **299** (R = H and Me), itself prepared by the reaction of an arylamine with the tricarbonyl-(cyclohexadienyl)iron cation, may have potential as a method.⁵⁵⁵

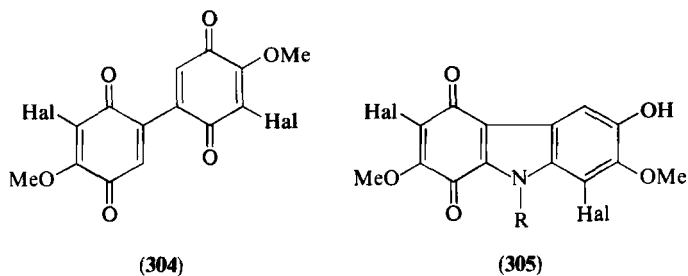
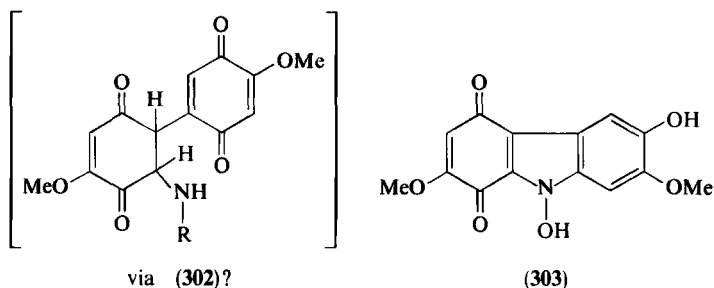
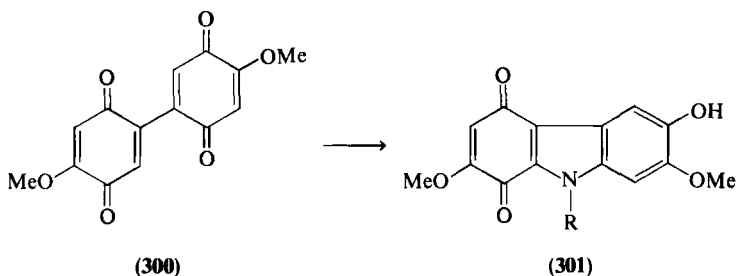


⁵⁵⁴ H. Stetter and M. Schwarz, *Justus Liebigs Ann. Chem.* **617**, 54 (1958).

⁵⁵⁵ A. J. Birch, A. J. Liepa, and G. R. Stephenson, *Tetrahedron Lett.*, 3565 (1979).

11. 2,2'-Di-*p*-benzoquinones

The diquinone **300** has been shown⁵⁵⁶⁻⁵⁵⁸ to react with a variety of primary amines producing carbazole quinones **301**, a process which presumably involves an intermediate such as **302** formed by Michael-type addition. Alkyl-,⁵⁵⁶ aryl-,⁵⁵⁶ and heteroaryl amines⁵⁵⁸ and amino acids⁵⁵⁷ have been utilized. The reaction failed with *p*-nitro- and *p*-acetylanilines⁵⁵⁹; neutral and acidic amino acids required base catalysis.^{557,559} Hydroxyl-



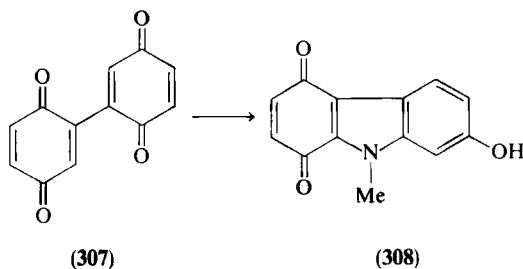
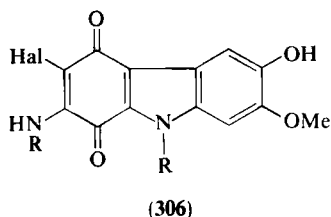
⁵⁵⁶ A. M. Osman and A. S. Hammam, *Egypt. J. Chem.* **15**, 213 (1972) [*CA* **80**, 4889w (1974)].

⁵⁵⁷ A. S. Hammam, *J. Appl. Chem. Biotechnol.* **26**, 667 (1976) [*CA* **86**, 171180p (1977)].

⁵⁵⁸ A. S. Hammam and H. S. El-Kasaf, *Rev. Roum. Chim.* **23**, 587 (1978) [*CA* **89**, 163481j (1978)].

⁵⁵⁹ A. S. Hammam, *Egypt. J. Chem.* **15**, 391 (1972).

amine gave the 9-hydroxycarbazolequinone **303**.⁵⁵⁹ The dihalodiquinones **304** (Hal = Cl or Br) reacted comparably producing **305**; the use of excess amine reportedly led to replacement of methoxyl, rather than halogen and the formation of **306**.⁵⁶⁰ The 2,2'-diquinone **307** gave carbazole quinone **308** on treatment with methylamine.²¹



C. FROM DIPHENYLAMINES

1. By Photochemical Reaction

In a preparatively useful process diarylamines can be cyclized photolytically.⁵⁶¹⁻⁵⁶⁵ Substrates having alkyl groups,^{561,562,564,566} fluorine,^{563,565} methoxyl,^{32,563,565} ethylamino,⁵⁶⁴ and N-alkyl^{563,564} and N-aryl^{563,565} groups have been used. Not all triarylamines could be cyclized, especially

⁵⁶⁰ A. M. Osman, A. S. Hammam, and H. S. El-Kasef, *Egypt. J. Chem.* **15**, 277 (1972).

⁵⁶¹ W. Caruthers, *J. Chem. Soc. C*, 2244 (1968); see also Y. Tsunashima, T. Sugimoto, and M. Kuroki, *J. Heterocycl. Chem.* **19**, 933 (1982).

⁵⁶² R. J. Olsen and O. W. Cummings, *J. Heterocycl. Chem.* **18**, 439 (1981).

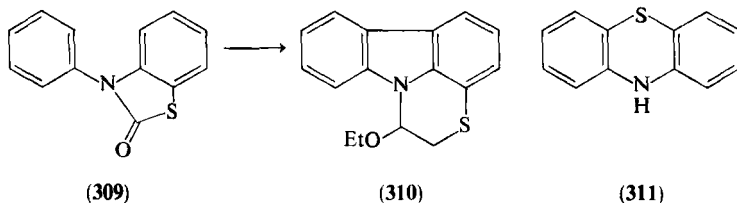
⁵⁶³ E. P. Fokin, T. N. Gerasimova, and T. V. Fomenko, U.S.S.R. Patent 527,424 [*CA* **86**, 72436v (1977)]; E. P. Fokin, T. N. Gerasimova, T. V. Fomenko, and N. V. Semikobeneva, *Zh. Org. Chem.* **14**, 834 (1978) [*CA* **89**, 42997y (1978)].

⁵⁶⁴ J.-D. Cheng and H. J. Shine, *J. Org. Chem.* **39**, 336 (1974).

⁵⁶⁵ W. Lamm, W. Jugelt, and F. Pragst, *J. Prakt. Chem.* **317**, 284 (1975).

⁵⁶⁶ C. Wentrup and M. Gaugaz, *Helv. Chim. Acta* **54**, 2108 (1971).

those in which one aryl group carried an electron-withdrawing group.⁵⁶⁵ Petrol has most often been used as a solvent. Oxygen has a deleterious effect on carbazole formation⁵⁶⁷⁻⁵⁶⁹ from diphenylamines, as diphenylnitroxide formation competes.^{568,569} However, the reverse is true for *N*-alkyldiphenylamines. *N*-(2-Cyanophenyl)aniline gives carbazole in high yield on photolysis in the absence of oxygen⁵⁷⁰; indazole, which serves as a precursor of the nitrile, also gives carbazole.⁵⁷⁰ The cyclic diphenylamide **309** on irradiation in vinyl ethyl ether gives a small amount of carbazole along with **310** (31%).⁵⁷¹ Thermolysis of **309** at 750°C produced 25% carbazole and 31% **311**.⁵⁷²



Considerable effort has been expended on elucidating the mechanism of the photocyclizations. Di-*p*-tolylamine can be cyclized to 3,6-dimethylcarbazole either photolytically in petrol or thermally at 880°C. Each process was viewed as electrocyclic, proceeding via *cis* and *trans* versions of **312** ($R^1 = \text{Me}$, $R^2 = \text{H}$) produced by dis- or conrotatory processes, respectively.⁵⁶⁶

Most mechanistic studies^{566,573-577} have utilized *N,N*-diphenylmethylamine. With this substrate in the absence of oxygen, photochemical cyclization to the observable **312** ($R^1 = \text{H}$, $R^2 = \text{Me}$) is followed by disproportionation to the carbazole and to a tetrahydrocarbazole believed to be

⁵⁶⁷ E. J. Bowan and J. H. D. Eland, *Proc. Chem. Soc., London*, 202 (1963).

⁵⁶⁸ W. R. Bansal, S. Puri, and K. S. Sidhu, *J. Indian Chem. Soc.* **52**, 308 (1975).

⁵⁶⁹ N. R. K. Santhanam, B. Sethuram, and T. N. Rao, *Indian J. Chem.* **12**, 422 (1974).

⁵⁷⁰ J. S. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.* **96**, 2010 (1974).

⁵⁷¹ L. R. Sousa and J. G. Bucher, *Tetrahedron Lett.*, 2267 (1978).

⁵⁷² D. Lin, M. Thomson, and D. De Jough, *Can. J. Chem.* **53**, 2293 (1975).

⁵⁷³ K. H. Grellmann, G. M. Sherman, and H. Linschitz, *J. Am. Chem. Soc.* **86**, 1881 (1963).

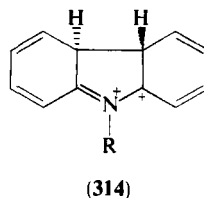
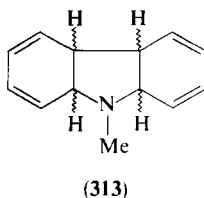
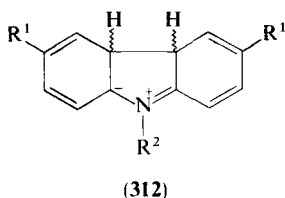
⁵⁷⁴ H. Linschitz and K. Heinz, *J. Am. Chem. Soc.* **86**, 303 (1964).

⁵⁷⁵ E. W. Förster, K. H. Grellmann, and H. Linschitz, *J. Am. Chem. Soc.* **95**, 3108 (1973), and references therein.

⁵⁷⁶ G. Fischer, E. Fischer, K. H. Grellmann, H. Linschitz, and A. Temizer, *J. Am. Chem. Soc.* **96**, 6267 (1974).

⁵⁷⁷ K. H. Grellmann, W. Kuehnle, H. Weller, and T. Wolff, *J. Am. Chem. Soc.* **103**, 6889 (1981), and references therein.

313.^{575,577} In the presence of oxygen the cyclized intermediate is oxidized to carbazole.



The anodic oxidative ring closure of diphenylamines in nonaqueous media is also believed to proceed by a process comparable in certain aspects. An initial dication is believed to then form **314** rapidly; loss of two protons gives the carbazole. In contrast to the photochemical process, some triarylamines carrying electron-withdrawing groups could be cyclized by this method; such species could not be cyclized photochemically due to reversion of triplet to ground state. The reported preparative yields of carbazoles in these electrolytic studies were low, and the substrates described were restricted to those having *p*-substituted rings.⁵⁷⁸

2. By Chemical Means

The oxidative closure of diphenylamines has been achieved with iodine at 350°C⁵⁷⁹ and with platinum at 450–540°C.⁵⁸⁰ Carbon-carbon bonding via displacement of the halogen of a 2-chlorophenyl-3'-hydroxyphenylamine clearly must involve intramolecular nucleophilic displacement para to phenoxide.⁵⁸¹

An efficient chemical process for closing a diphenylamine is that using palladium(II) acetate (2 mol for substrates carrying electron-withdrawing groups) in acetic acid-methanesulfonic acid. Carbazole formation has been achieved with alkyl-, halo-, nitro-, and carboxyl-substituted diphenylamines. 1-Chlorocarbazole and carbazol-1-yl carboxylic acid as examples were efficiently prepared.⁵⁸² This is probably the best method now available for cyclizing diphenylamines.

⁵⁷⁸ R. Reynolds, L. L. Line, and R. F. Nelson, *J. Am. Chem. Soc.* **96**, 1087 (1974).

⁵⁷⁹ A. Islam, P. Bhattacharyya, and D. P. Chakraborty, *J. C. S. Chem. Commun.*, 537 (1972).

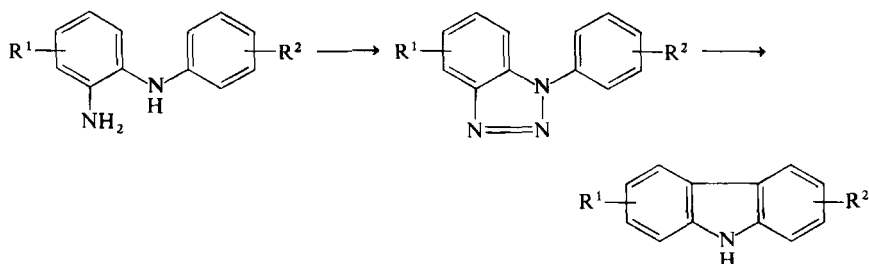
⁵⁸⁰ M. Naito, K. Murayama, and M. Matsumoto, *Aromatikkusu* **32**, 39 (1980) [*CA* **93**, 204397g (1980)].

⁵⁸¹ F. Werner, R. Puetter, and P. Wenzel, German Patent 2,711,943 [*CA* **90**, P6246q (1979)].

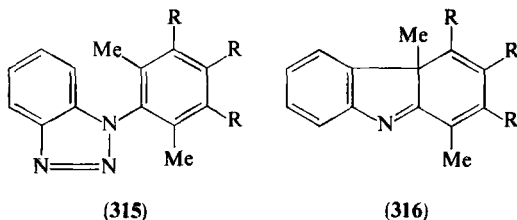
⁵⁸² B. Akermark, L. Eberson, E. Jonsson, and E. Pettersson, *J. Org. Chem.* **40**, 1365 (1975).

3. Via Benzotriazoles: The Graebe-Ullmann Reaction

The diazotization of a 4-(2-aminoaryl)arylamine produces a 1-arylbenzotriazole. Thermal^{50,341,583-588} (generally about 350°C) or photochemical⁵⁸⁹⁻⁵⁹² elimination of nitrogen generates a species which on cyclization gives a carbazole. This is the classic Graebe-Ullmann reaction, which has been shown in recent examples to tolerate the presence of alkyl,^{341,583,584,586} nitro,⁵⁸⁵⁻⁵⁸⁷ halogeno,⁵⁰ alkylsulfonyl,⁵⁸⁷ alkoxy,^{584,588} and cyano⁵⁸⁸ groups. 1-Cyclohexylbenzotriazole gave 15% of carbazole on heating at 400°C.⁵⁹³



At higher temperatures than those usually employed, flash vacuum pyrolysis (640°C) of the doubly ortho-blocked benzotriazole **315** (R = H) gave 1,4-dimethylcarbazole (30%), 1-methylcarbazole (35%) and 1,8-dimethylcarbazole, each product thought to arise by rearrangement of intermediate **316** (R = H).⁵⁹⁴ Photolytic cleavage of **315** (R = Me) giving 1,2,3,4-tetramethyl-



⁵⁸³ V. Vaníček and Z. J. Allan, *Chem. Listy* **48**, 1705 (1954).

⁵⁸⁴ R. Kreher and W. Gerhardt, *Tetrahedron Lett.*, 3465 (1977).

⁵⁸⁵ B. Stárková, A. Vystrčil, and L. Stárka, *Collect. Czech. Chem. Commun.* **22**, 1019 (1957).

⁵⁸⁶ H. Sieper, *Chem. Ber.* **100**, 1646 (1967).

⁵⁸⁷ E. Balicka and Z. Eckstein, *Rocz. Chem.* **49**, 1927 (1975) [*CA* **84**, 105497e (1976)].

⁵⁸⁸ J. P. Henichart, J. L. Bernier, C. Vaccher, R. Houssin, V. Warin, and F. Baert, *Tetrahedron* **36**, 3535 (1980).

⁵⁸⁹ J. H. Boyer and R. Selvarajan, *J. Heterocycl. Chem.* **6**, 503 (1969).

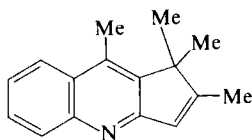
⁵⁹⁰ E. M. Burgess, R. Carithers, and L. McCullagh, *J. Am. Chem. Soc.* **90**, 1923 (1968).

⁵⁹¹ M. Ohashi, K. Tsujimoto, and T. Yonezawa, *Chem. Commun.*, 1089 (1970).

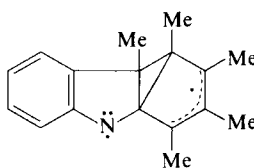
⁵⁹² H. Murai, M. Torres, and O. P. Strausz, *J. Am. Chem. Soc.* **102**, 1421 (1980).

⁵⁹³ B. W. Ashton and H. Suschitzky, *J. Chem. Soc.*, 4559 (1957).

⁵⁹⁴ J. J. Kulagowski, C. J. Moody, and C. W. Rees, *J. C. S. Chem. Commun.*, 548 (1982).



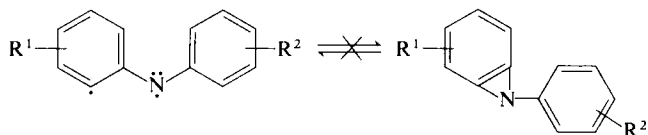
(317)



(318)

carbazole (18%) along with the quinoline **317** (20%) was pictured as also involving an intermediate of the same type (**316**; R = Me), then transformed with light into **318** and thus to products.⁵⁹⁴

Photolytic decomposition of 1-arylbenzotriazoles gives a species on loss of nitrogen that is best viewed as diradical **319**; a low barrier to rotation allows the correct alignment of the two aromatic rings to be achieved without interference from side reactions.^{590,592} Equilibration with **320** was shown not to be involved because 3,6-dichlorocarbazole and not its 2,6-isomer were formed using **321** (R¹ = R² = 4-Cl).⁵⁹¹

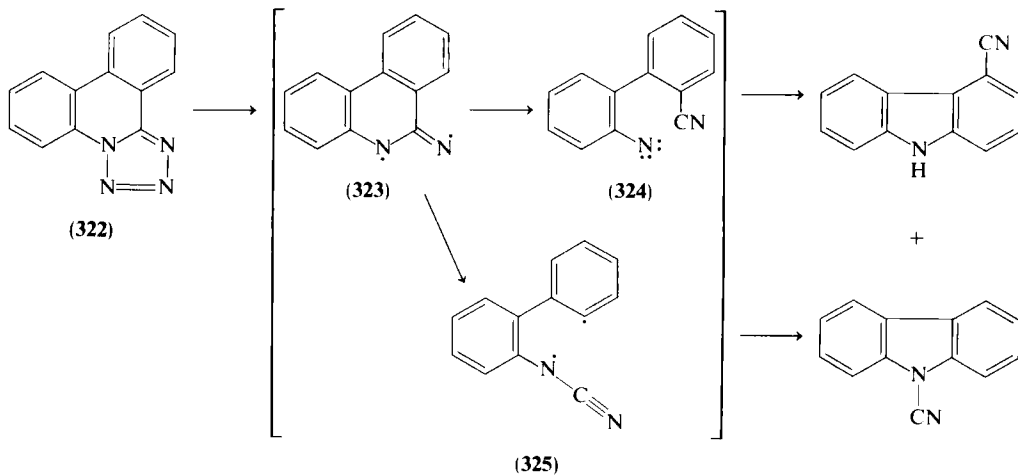


(319)

(320)

(321) R¹ = R² = 4-Cl

The 500°C thermolysis of the tetrazole **322** gave 9-cyanocarbazole (10%) and a good yield (60%) of 4-cyanocarbazole; the process is thought to proceed via diradical **323** and nitrene **324** to explain the formation of 9-cyanocarbazole and via **325** to rationalize the minor product.¹⁵⁵



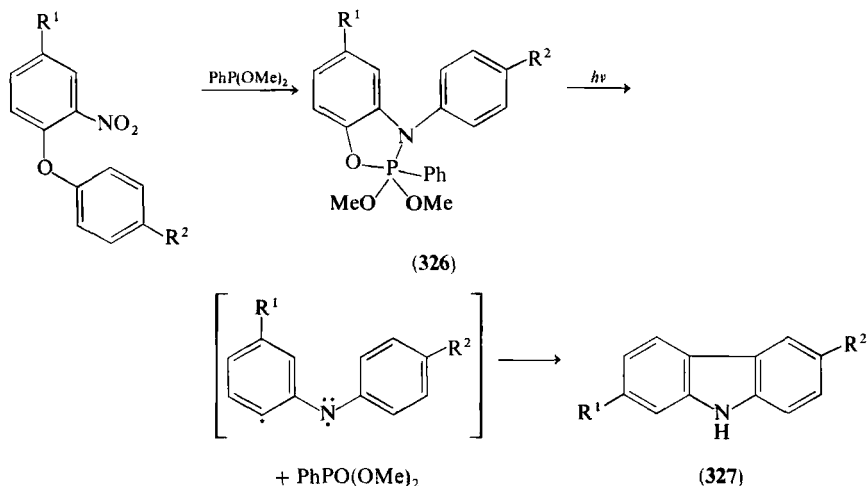
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In a process viewed as the phosphorus analog of the Graebe–Ullmann reaction, photolysis of phopholines **326** ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = OMe$; $R^1 = Me$, $R^2 = OMe$) gave dimethylphenyl phosphate and carbazoles **327** via the presumed diradical intermediate shown.⁵⁹⁵



D. FROM TWO SEPARATE SIX-MEMBERED RING COMPONENTS

Aniline heated at 350°C with a trace of iodine gave 25% of carbazole.⁵⁹⁶ *o*-Ethyl-*N*-methylaniline heated with Raney nickel at 230°C gave a trace of carbazole as well as many other products.⁵⁹⁷ Nitrobenzene heated at 600°C also gave a trace of carbazole and many other products.⁵⁹⁸

The generation of benzyne in the presence of nitrosobenzene produced 45% of 9-phenylcarbazole; the process may proceed via 9-hydroxycarbazole, as shown, with final loss of oxygen in some manner. The production of 3-bromo-9-phenylcarbazole from 4-bromonitrosobenzene substantiates the sequence proposed,⁵⁹⁹ as does the observation that tetrabromo- (and tetrachloro-) benzyne react with nitrobenzenes to produce low to moderate yields of tetrahalo-9-hydroxycarbazoles.⁶⁰⁰

The thermal decomposition of diazotized anthranilic acid in acetone led to carbazole **328** as well as to **329**, benzoic acid, and *o*-biphenylene. The **329**

⁵⁹⁵ J. I. G. Cadogan, B. S. Tait, and N. J. Tweddle, *J. C. S. Chem. Commun.*, 847 (1975).

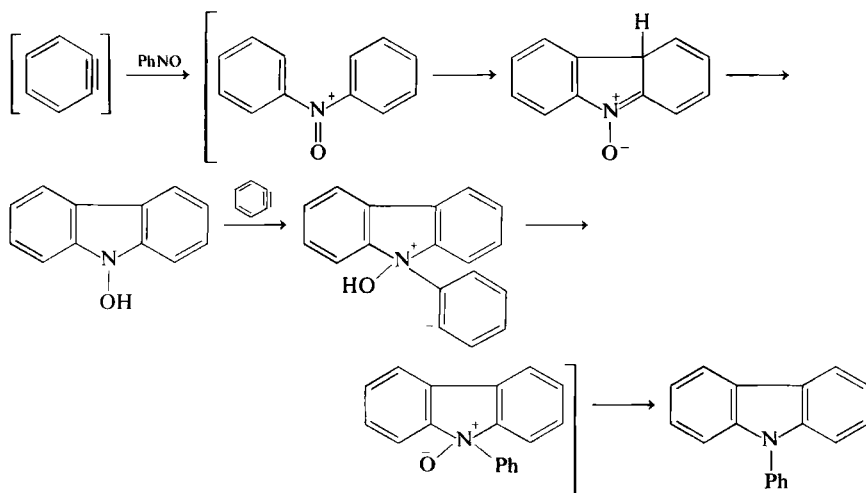
⁵⁹⁶ D. P. Chakraborty, M. Sarkar, and A. Islam, *J. Indian Chem. Soc.* **56**, 1217 (1979).

⁵⁹⁷ G. D. F. Jackson and W. H. F. Sasse, *Aust. J. Chem.* **17**, 337 (1964).

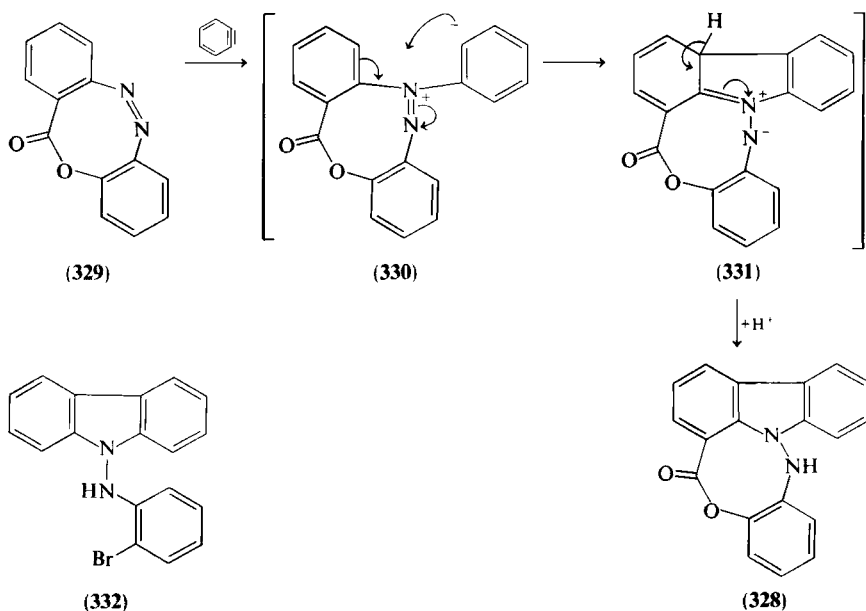
⁵⁹⁸ E. K. Fields and S. Meyerson, *J. Am. Chem. Soc.* **89**, 3224 (1967).

⁵⁹⁹ G. W. Steinhoff and M. C. Henry, *J. Org. Chem.* **29**, 2808 (1964).

⁶⁰⁰ P. C. Buxton, H. Heaney, K. G. Mason, and J. M. Skatchley, *J. C. S. Perkin I*, 2695 (1974).



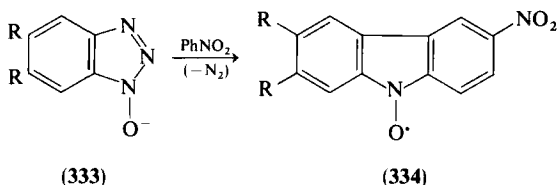
formed initially reacts with benzyne through intermediates **330** and **331** giving **328**.⁶⁰¹ When the hydrobromide salt of diazotized anthranilic acid was heated in 1,2-dichloroethane and propylene oxide a small amount of carbazole **332** was formed⁶⁰² (without the propylene oxide the reaction did not occur).



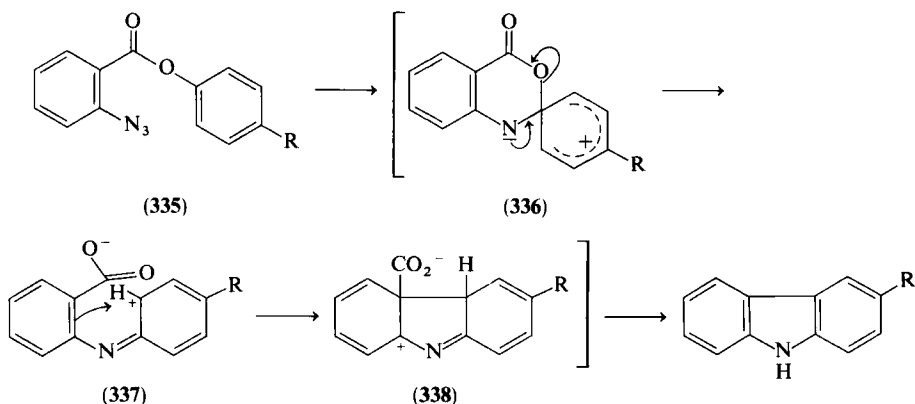
⁶⁰¹ T. Miwa, M. Kato, and T. Tamano, *Tetrahedron Lett.*, 2743 (1968).

⁶⁰² R. Ghosh, E. B. Sheinim, C. L. Bell, and L. Bauer, *J. Heterocycl. Chem.* **12**, 203 (1975).

Loss of nitrogen from the nitroxides **333** ($R = H, NO_2$, or OMe) in the presence of aromatic compounds such as nitrobenzene gave carbazole nitroxides, for example, **334** ($R = H, NO_2$, and OMe).⁶⁰³



Vapor phase pyrolyses (400–550°C) of the azido esters **335** ($R = H, Me, Cl, Br$, or CO_2Et) gave yields of about 50% of the 3- R -substituted carbazoles. This sequence can be explained using intermediates **336** and **337** and final loss of carbon dioxide from **338**.⁶⁰⁴



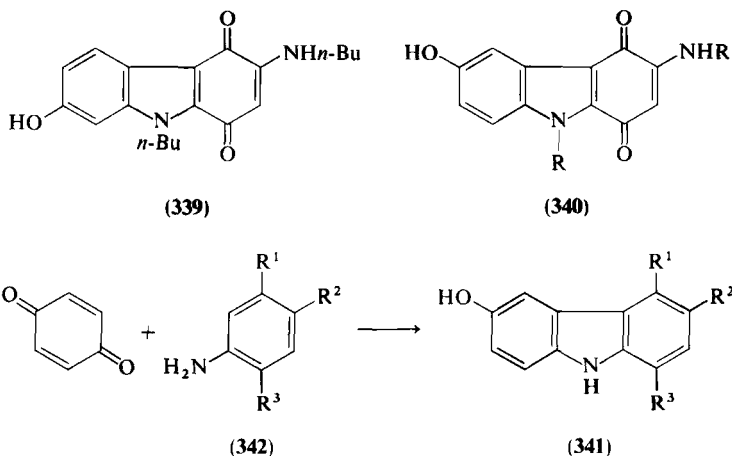
p-Benzoquinone was reported to produce a low yield of the carbazole-quinone **339** on reaction with *n*-butylamine.⁶⁰⁵ However, later work with carbazole quinones produced with methylamine, propylamine, benzylamine, and ethanolamine accorded structures **340**, seemingly more in line with a reasonable mechanistic sequence for their formation.²¹ 3-Hydroxycarbazoles **341** in low yields accompanied by other products resulted from the Nenitzescu-like interaction of *p*-benzoquinone with variously substituted aromatic amines (**342**: $R^1 = R^3 = H, R^3 = NO_2; R^1 = R^3 = Me, R^2 = NO_2; R^1 = R^3 = Me, R^2 = CN$).⁶⁰⁶

⁶⁰³ H. G. Aurich, G. Bach, K. Hahn, G. Kuettner, and W. Weiss, *J. Chem. Res., Synop.*, 122; *J. Chem. Res.*, Miniprint, 1544 (1977).

⁶⁰⁴ M. G. Clancy, M. M. Hesabi, and O. Meth-Cohn, *J. C. S. Chem. Commun.*, 1112 (1980).

⁶⁰⁵ K. Sugita and J. Kumanotani, *Bull. Chem. Soc. Jpn.* **42**, 2043 (1969).

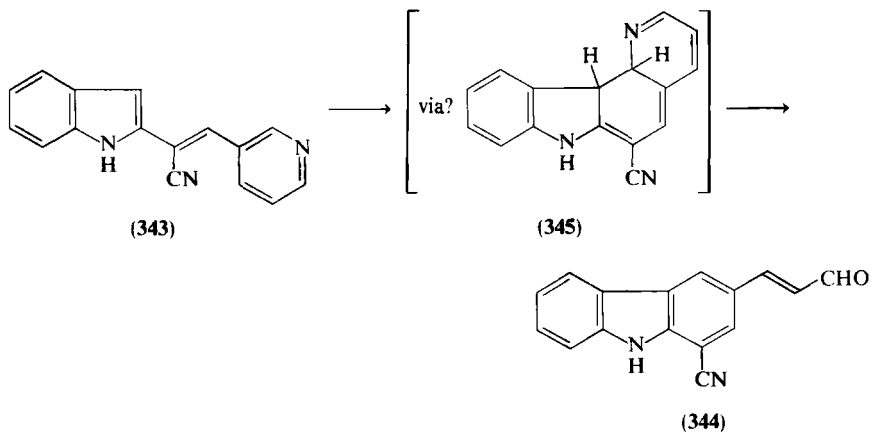
⁶⁰⁶ J. L. Bernier, J. P. Hénichart, C. Vaccher, and R. Houssin, *J. Org. Chem.* **45**, 1493 (1980).



E. FROM INDOLES

1. The 4,4a-bond

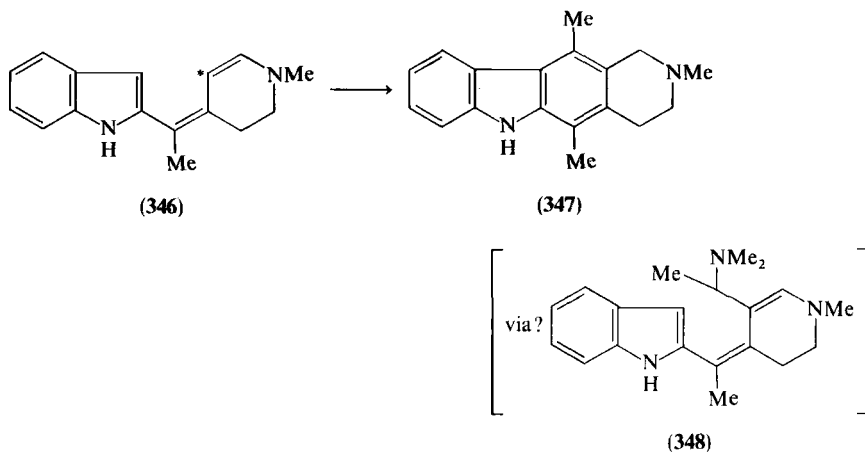
Photolysis of **343** in the absence of oxygen gave, among other products, the carbazole aldehyde **344**; **345** may be an intermediate.⁶⁰⁷



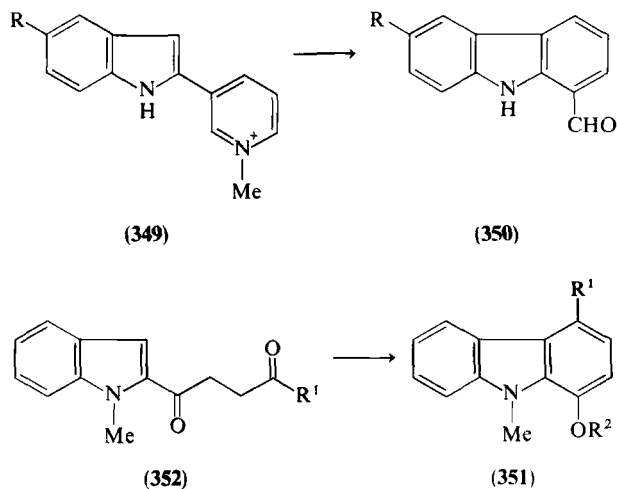
The dienamine **346** on treatment with acetaldehyde–dimethylamine–acetic acid gave a small yield of carbazole **347**. This process may proceed via

⁶⁰⁷ H.-P. Husson, C. Thal, P. Potier and E. Wenkert, *J. Org. Chem.* **35**, 442 (1970).

electrophilic attack at C* of the enamine, producing **348** now set up for electrophilic closure onto the indole β -position. An alternative is initial dimethylaminoethylation at the indole β -position.⁶⁰⁸



Perhaps more general are the transformations of pyridinium salts **349** ($\text{R} = \text{H}$, Me, or Br) into the 1-formylcarbazoles **350** in aqueous base.⁶⁰⁹ Several 1-hydroxy- or 1-alkoxy-4-alkylcarbazoles (**351**) were prepared via



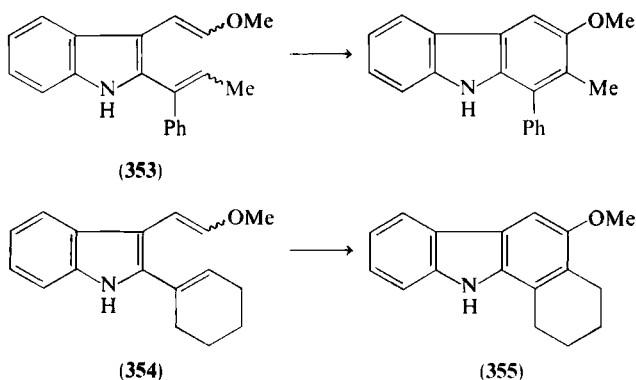
⁶⁰⁸ R. Besselièvre, C. Thal, H.-P. Husson, and P. Potier, *J. C. S. Chem. Commun.*, 90 (1975).

⁶⁰⁹ A. N. Kost, T. V. Stupnikova, R. S. Sagitullin, B. P. Zemskii, and A. K. Sheinkman, *Dokl. Akad. Nauk SSSR* **244**, 103 (1979) [*CA* **90**, 137618k (1979)].

the diketones **352** ($R^1 = \text{Me}$ or Ph) on reaction with acid⁶¹⁰ in an alcohol ($R^2\text{OH}$).

2. The 2,3-Bond

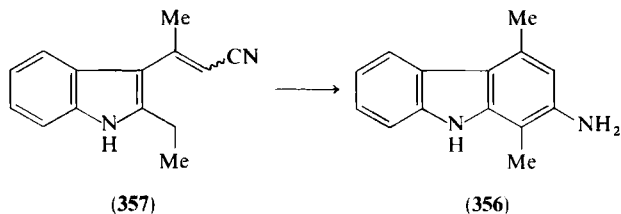
Electrocyclic closure of "triene" **353** in the presence of palladium-charcoal as a dehydrogenating agent produced 1-phenyl-2-methyl-3-methoxycarbazole,⁶¹¹ and an analogous process converted **354** to **355**.⁶¹²



3. The 1,2-Bond

1,4-Dimethyl-2-aminocarbazole (**356**) was easily prepared by treating **357** with sodium hydride in diphenyl ether at 220°C.³¹⁰

The condensation product (**358**) from 1,2-dimethyl-3-formylindole and Meldrum's acid gave 2-hydroxy-9-methylcarbazole on flash vacuum pyrolysis at 500°C, probably via **359**.⁶¹³

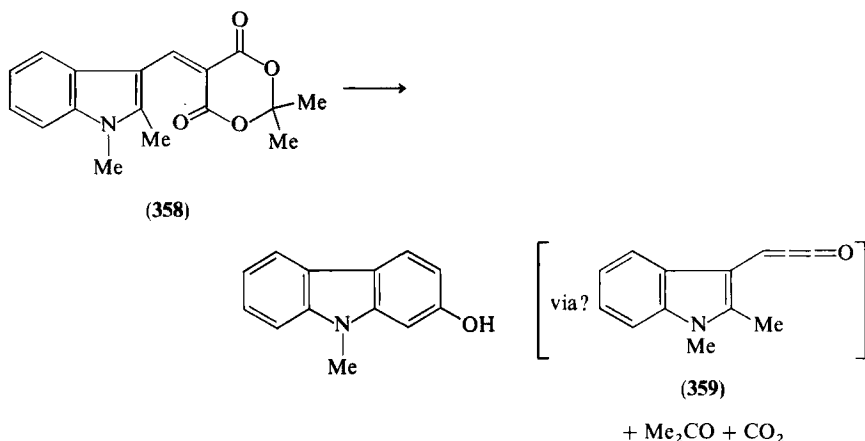


⁶¹⁰ H. Stetter and P. Lappe, *Chem. Ber.* **113**, 1890 (1980).

⁶¹¹ S. Kano, E. Sugino, and S. Hibino, *J. C. S. Chem. Commun.*, 1241 (1980).

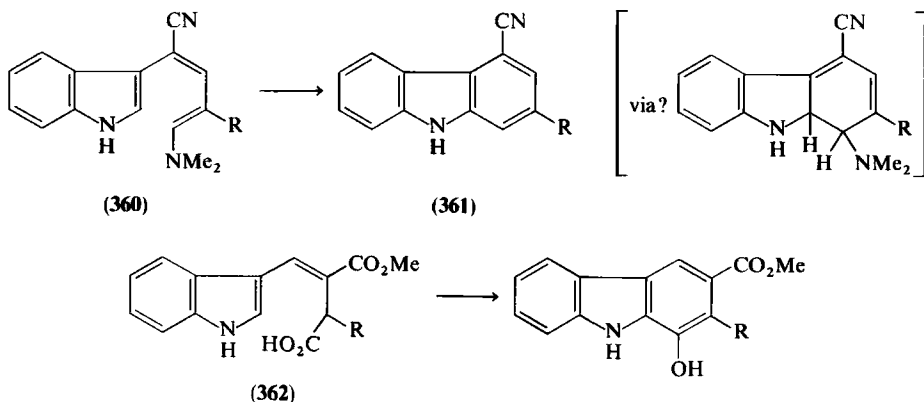
⁶¹² S. Kano, E. Sugino, S. Shibuya, and S. Hibino, *J. Org. Chem.* **46**, 3856 (1981).

⁶¹³ G. J. Baxter, R. F. C. Brown, and G. L. McMullen, *Aust. J. Chem.* **27**, 2605 (1974).



4. The 9a,1-Bond

The thermal cyclization of the indol-3-ylidienamines **360** (R = H, Ph, or OH), which gave the 4-cyanocarbazoles **361**, are presumably driven to completion by the loss of dimethylamine.⁶¹⁴ Intramolecular indole α -acylation using ester acids (**362**; R = H or Me) produced by Stobbe condensation gave

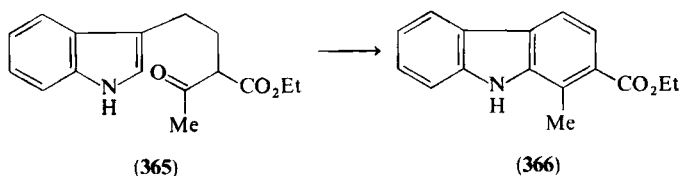
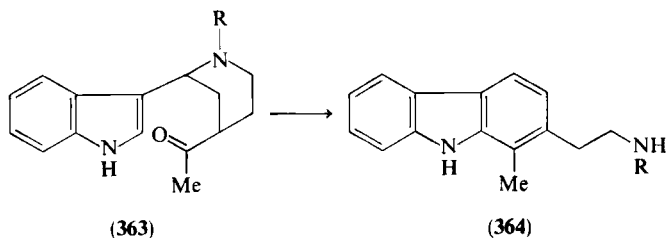


1-hydroxycarbazole-3-esters.⁶¹⁵ In another intramolecular indole α -substitution, the protonated carbonyl group of **363** (R = PhCO or Me) served as an electrophile, and this was followed by 1,2-elimination of the nitrogen

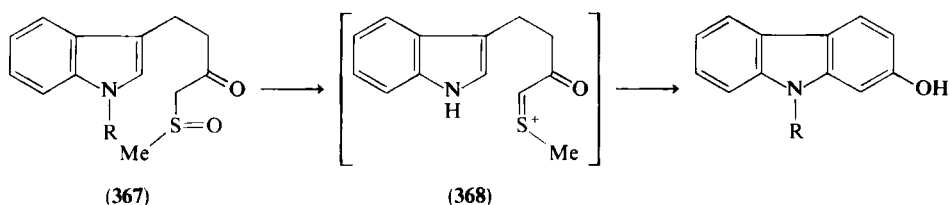
⁶¹⁴ C. Jutz and R. M. Wagner, *Angew. Chem., Int. Ed. Engl.* **11**, 315 (1972).

⁶¹⁵ N. R. El-Rayyes, *J. Prakt. Chem.* **316**, 386 (1974).

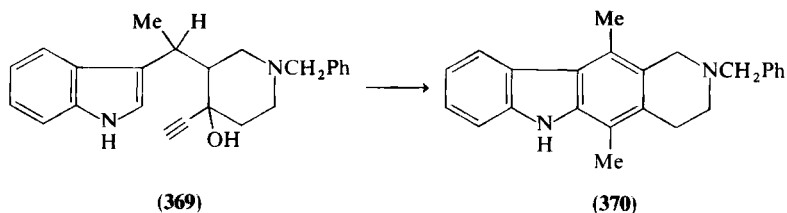
to give the carbazoles **364**.³⁵² Acid treatment of the keto ester **365** gave a mixture of ethyl 1-methylcarbazole-2-carboxylate (**366**) and its tetrahydro derivative by disproportionation. Carrying out the acid-catalyzed closure in the presence of chloranil produced only the carbazole.⁴⁰⁴



The sulfones **367** ($R = H$ and Me) obtained from 3-(indol-3-yl)propionate esters with the anion of dimethyl sulfoxide were cyclized, losing methylthiol, via **368** in the presence of *p*-toluenesulfonic acid in hot acetonitrile.⁴⁹⁸



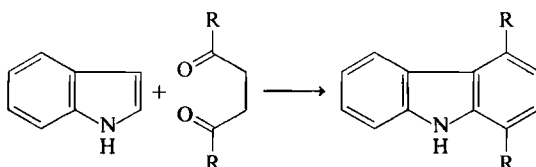
Finally, in this category is the closure promoted by formic acid of the acetylenic alcohol **369** to the carbazole **370**.⁶¹⁶



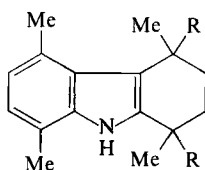
⁶¹⁶ F. Le Goffic, A. Gouyette, and A. Ahond, *Tetrahedron* **29**, 3357 (1973).

5. The 9a,1- and 4,4a-Bonds

Considerable use has been made of the carbazole synthesis^{171,313-317,320,321,341,490,617,618,619} that utilizes the acid- or Lewis acid-catalyzed double condensation of a 1,4-diketone with 2,3-unsubstituted indoles. 1,4-Dialkyl or diaryl substituted carbazoles of relevance to the synthesis of the alkaloid ellipticine and analogs are formed. The synthesis has been achieved with methyl,^{315,341,619} alkoxy,^{314-317,321} fluoro,³²⁰ bromo,³¹⁵ and nitro³¹⁵ substituents on the aromatic ring of the indole and with hexane-2,5-dione,^{313-317,320,321,341,490,618,619} 1-phenylpentane-1,4-dione,^{490,617} 1,4-diphenylbutane-1,4-dione,^{171,617} 3,4-dimethylhexane-2,5-dione, and 1,2,4-triphenylbutane-1,4-dione,⁶¹⁷ and levulin aldehyde dimethyl acetal.⁴⁹⁰ 1,3-Dimethylindole and hexane-2,5-dione gave some 1,4,9-trimethylcarbazole.⁶¹⁸



Pyrrole and hexane-2,5-dione in acetic acid in the presence of zinc acetate produced some 1,4,5,9-tetramethyl carbazole, although the main product was **371**.⁶¹⁹



(371) R = 2-indolyl

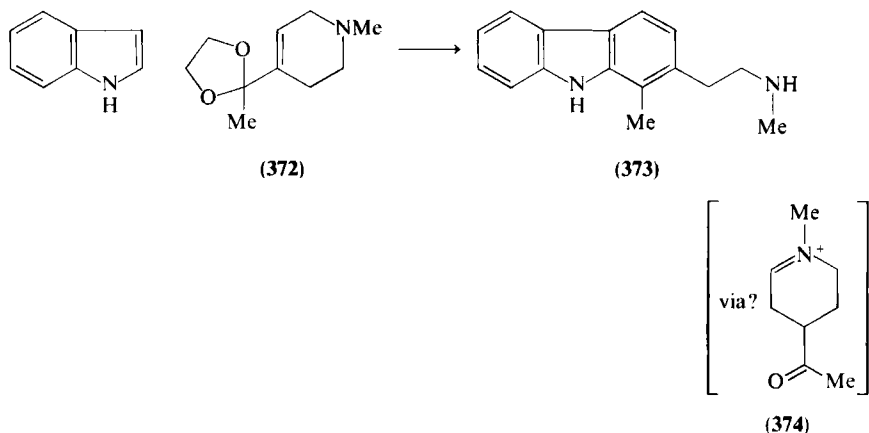
Indole and acetal **372** gave the carbazole **373** in 50% yield in acetic acid.⁶²⁰ It seems likely that conjugated ketone formed *in situ* isomerizes in two steps to the species **374** that initiates ring formation by attack at the indole β -position.

⁶¹⁷ E. Ritchie and W. C. Taylor, *Aust. J. Chem.* **24**, 2137 (1971).

⁶¹⁸ R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 2596 (1953).

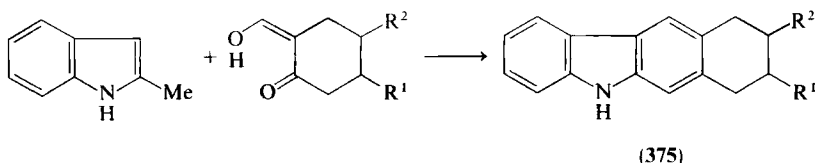
⁶¹⁹ L. K. Dalton and T. Teitei, *Aust. J. Chem.* **21**, 2053 (1968).

⁶²⁰ R. Besselièvre and H.-P. Husson, *Tetrahedron Lett.*, 1873 (1976).



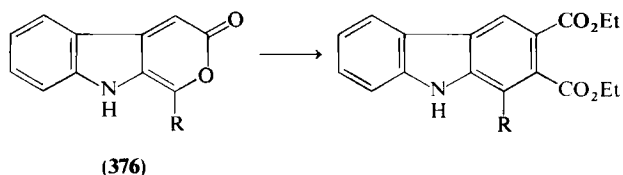
6. The 1,2- and 4,4a-Bonds

2-Methylindole condenses with methyl vinyl ketone in acetic acid-acetic anhydride in the presence of hydroquinone to produce 10% 2-methylcarbazole⁶²¹ and with 2-hydroxymethylene cyclohexanones to produce tetracycles **375** ($R^1 = R^2 = H$; $R^1 = \text{Me}$, $R^2 = H$; $R^1 = H$, $R^2 = \text{Me}$) in moderate yields. 1,2-Dimethylindole reacts comparably.⁶²²



7. The 1,2- and 3,4-Bonds

The indole α -pyrones **376** ($R = \text{Me}$ or Et) acted as dienophiles with diethylacetylenedicarboxylate producing the 1-substituted carbazole-2,3-diester in good yield by loss of carbon dioxide from the initial adduct.⁶²³

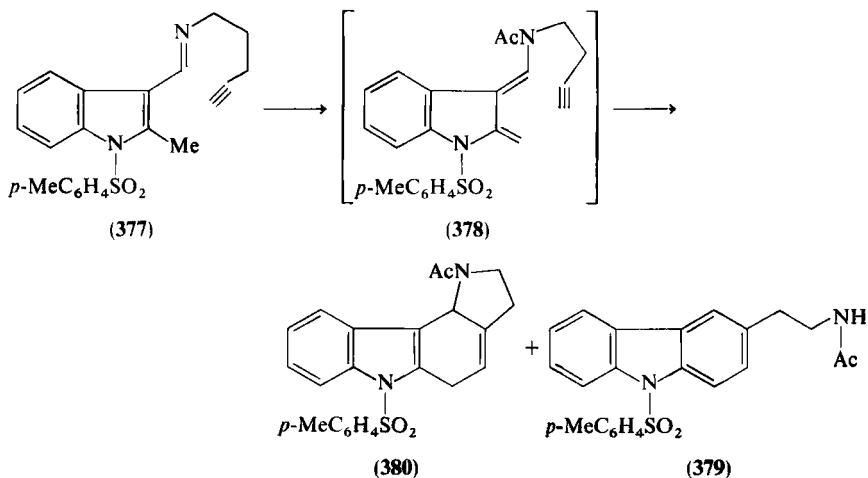


⁶²¹ J. Szmuszkovicz, *J. Am. Chem. Soc.* **79**, 2819 (1957).

⁶²² W. E. Noland and J. E. Johnson, *Tetrahedron Lett.*, 589 (1962).

⁶²³ H. Plieninger, W. Mueller, and K. Weinerth, *Chem. Ber.* **97**, 667 (1964).

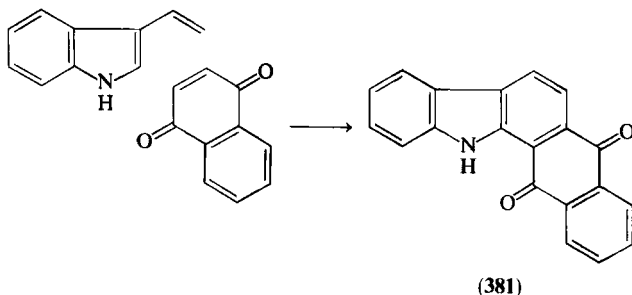
An intramolecular cycloaddition brought about by reaction with acetyl chloride and di-isopropylamine converted the imine **377**, presumably via **378**, to a mixture of the carbazole **379** and the tetracycle **380**; prolonged heating alone or brief treatment of the latter with *p*-toluenesulfonic acid caused elimination and the formation of **379**.⁶²⁴



1-Methylindole-2,3-dicarboxaldehyde condensed with 1,2-dibenzoyl-ethane forming 2,3-dibenzoyl-9-methylcarbazole.⁶²⁵

8. The 9a,1- and 2,3-Bonds

3-Vinylindole combines in a Diels-Alder fashion with nitroethene to produce 1-nitrocarbazole, although in very low yields. It does, however, produce a high yield of quinone **381** by reaction with naphthoquinone.⁶²⁶

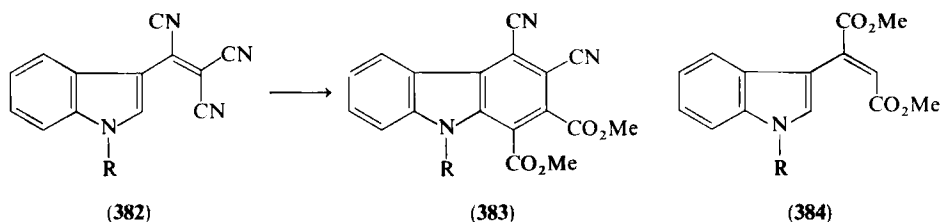


⁶²⁴ C. Exon, T. Gallagher, and P. Magnus, *J. C. S. Chem. Commun.*, 613 (1982)

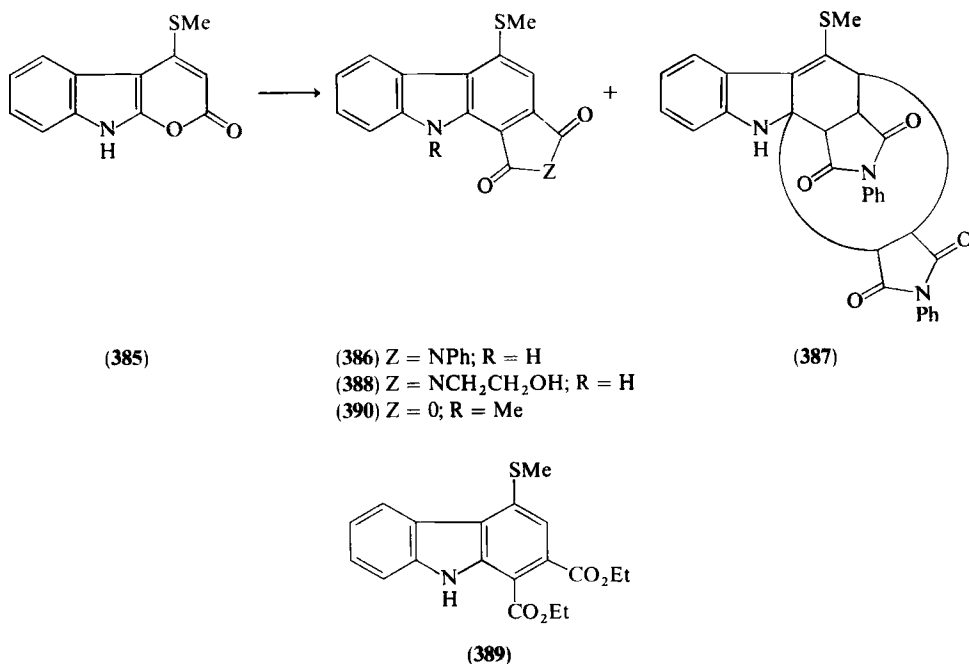
⁶²⁵ G. Dupas, J. Dufflos, and G. Quéguiner, *J. Heterocycl. Chem.* **17**, 93 (1980).

⁶²⁶ W. E. Noland and R. J. Sundberg, *J. Org. Chem.* **28**, 884 (1963).

The tricyanovinylindoles **382** ($R = H$ or Me) gave the dicyano diesters **383** ($R = H$ or Me) on reaction at high temperature.⁴³³ The (*E*)-diester **384** ($R = Me$) gave, with diethyl acetylenedicarboxylate, triethyl 9-methylcarbazole-1,2,4-tricarboxylate as a major product.⁶²⁷

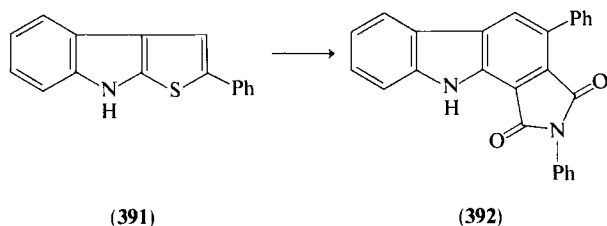


In other Diels-Alder additions, indolopyrone **385** reacted with *N*-phenylmaleinimide giving 10% of the carbazole **386** and 40% of **387** formed by a second addition. The latter was transformed into the carbazole **388** by heating in ethanolamine. Diethylacetylenedicarboxylate reacted simply with **385** producing the diester **389**, and the *N*-methyl analog of **385** gave **390** with



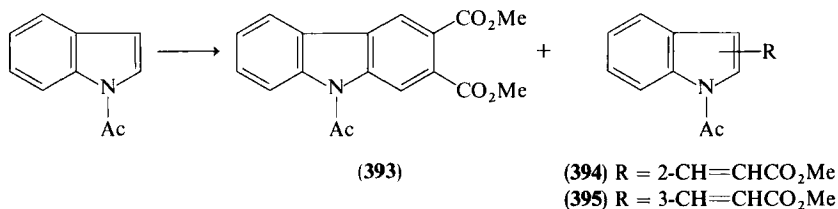
⁶²⁷ R. M. Acheson, J. N. Bridson, T. R. Cecil, and A. R. Honds, *J. C. S. Perkin I*, 1569 (1972).

maleic anhydride.⁶²⁸ The thienoindole **391** produced carbazole **392** with *N*-phenylmaleinimide but the adduct formed with diethylacetylenedicarboxylate did not lose sulfur and did not aromatize.⁶²⁹



9. The 9*a*,1-, 2,3-, and 4,4*a*-Bonds

Indole reacts with dimethylacetylene dicarboxylate giving tetramethylcarbazol-1,2,3,4-tetracarboxylate as a major product,^{433,627} formed via **384** (R = H, and/or geometric isomer) and then Diels–Alder addition and dehydrogenation.⁶²⁷ *N*-Acetylindole undergoes an extraordinary double condensation and cyclization with methyl acrylate in the presence of palladium(II) acetate in acetic acid giving 9% of the dimethyl 9-acetylcarbazole-2,3-dicarboxylate **393** as well as **394** and **395**, the products of monosubstitution at the indole α and β -positions.⁶³⁰



10. Miscellaneous

2,3-Cyclopentanoindole on vapor-phase pyrolysis in chloroform gave carbazole, 3-chlorocarbazole, and 4-chlorocarbazole (28:59:13) in 24% overall yield.⁶³¹

⁶²⁸ G. Kobayashi, S. Furukawa, Y. Matsuda, and R. Natsuki, *Yakugaku Zasshi* **88**, 767 (1968) [*CA* **70**, 3728z (1969)].

⁶²⁹ G. Kobayashi, S. Furukawa, Y. Matsuda, and R. Natsuki, *Yakugaku Zasshi* **89**, 58 (1969) [*CA* **70**, 96665q (1969)].

⁶³⁰ Y. Fujiwara, O. Maruyama, M. Yoshidomi, and H. Taniguchi, *J. Org. Chem.* **46**, 851 (1981).

⁶³¹ R. E. Busby, S. M. Hussain, M. Uqbal, M. A. Khan, J. Parrick, and C. J. G. Shaw, *J. C. S. Perkin I*, 2783 (1979).

Four-Membered Rings Containing One Sulfur Atom

WALTER RIED and BETTINA HEINZ

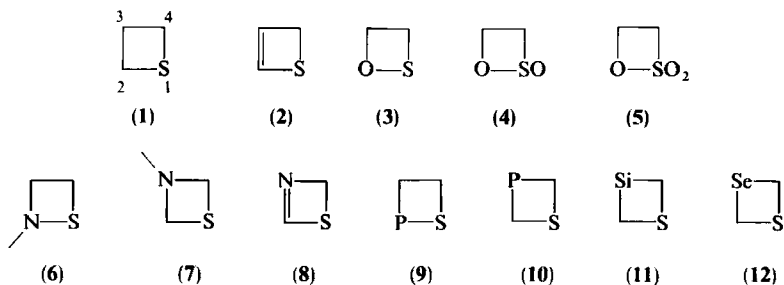
*Institute of Organic Chemistry, Frankfurt am Main,
Federal Republic of Germany*

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I. Introduction

The present review is concerned with four-membered heterocycles that contain one sulfur atom either alone or associated with another heteroatom. The classes of compounds that will be discussed are the thietanes (1) and thietes (2), the 1,2-oxathietanes (3), the β -sultines and β -sultones (4 and 5), the 1,2- and 1,3-thiazetidines (6 and 7) and thiazetes (8), the 1,2- and 1,3-thiaphosphetanes (9 and 10), and the 1,3-silathietanes and 1,3-selenathietanes (11 and 12).



Literature published prior to 1965 is not emphasized, unless there is some obvious relevance to later work. For earlier references, consult the extensive review on thietanes by Sander.¹ A book on three- and four-membered het-

¹ M. Sander, *Chem. Rev.* **66**, 341 (1966).

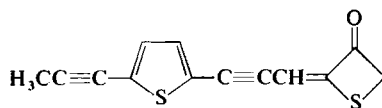
erocycles has been written by Etienne and co-authors² in 1964. Reviews dealing with four-membered heterocyclic compounds that may contain other heteroatoms are presented as specialist reports in "Organic Compounds of Sulfur, Selenium and Tellurium."³ The literature is covered up through 1980; a list of references up to 1983 is presented.

The prime concern of this article is to shed light on the modes of synthesis, applications, and the chemical behavior of the title compounds. Theoretical aspects of stereochemistry, spectroscopy, and quantum chemistry are considered to a minor degree.

II. Occurrence and Uses

Thietanes and 3-thietanones represent the only four-membered sulfur-containing heterocycles of the title group that have been isolated from natural sources. Even in petroleum deposits, where 5- and 6-membered cyclic sulfur compounds are common, thietanes occur only in small amounts.⁴ However, thiacyclobutane (**1**) and thiacyclopentane are both commonly found in shale oil and could be utilized as a possible source of fuel.⁵

Thietane compounds could occur in space especially when one considers that sulfine, a commonly observed pyrolysis fragmentation product of thietane oxide, has been detected in the interstellar medium by microwave spectroscopy.⁶ Thietane derivatives have been isolated from the plant and animal kingdom, and it seems likely that much still remains untapped. In such plants as *Tribus Arctotideae*, the thioacetylene structure **13** containing a 3-



(13)

thietanone as well as a thiophene ring was ascertained by spectroscopic methods and by synthesis.⁷ Alkylated thietane derivatives such as 2,2-dimethylthietane (**Mustelan**) (**14**) have been extracted from the malodorous

² Y. Etienne, R. Soulas, and H. Lumbroso, *Chem. Heterocycl. Comp.* **19**, 647 (1964).

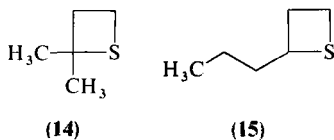
³ D. H. Reid, ed., "Organic Compounds of Sulphur, Selenium, and Tellurium," *Spec. Period. Rep. Chem. Soc.*, London.

⁴ E. V. Whitehead, Z. T. Dean, and F. A. Fiedler, *J. Am. Chem. Soc.* **73**, 3632 (1951).

⁵ F. P. Miknis and J. P. Biscac, *J. Phys. Chem.* **75**, 725 (1971).

⁶ E. Block, R. Penn, R. J. Olsen, and P. Shewin, *J. Am. Chem. Soc.* **98**, 1264 (1976).

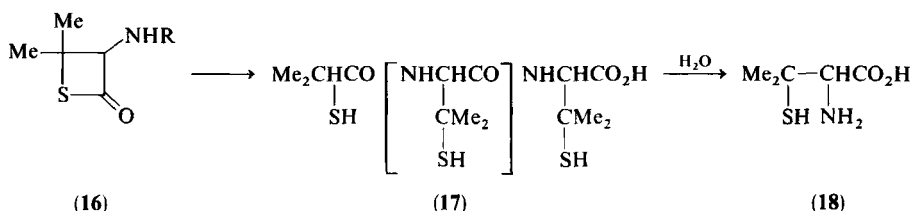
⁷ F. Bohlmann and W. Skuballa, *Chem. Ber.* **106**, 497 (1973).



anal secretory fluids of the mink (*Mustela vison*)⁸ and 2-propylthietane (15) from the stoat (*Mustela erminea*).⁹

Pharmaceutical studies of the thietane 1,1-dioxides are being undertaken in relation to analgesic activity¹⁰ because they can be viewed as conformationally restricted analogs of diphenylpropylamine-type analgesics. Thietane 1,1-dioxides have also been considered as potential methadone analgesics.¹¹

The amino-2-thietanone 16 is a latent form of penicillamine (18) and is thus biologically interesting.¹² The ring-opened polymer (17) of this thietanone monomer yields penicillamine on hydrolysis.



Thietane and thiophene deposits in shale oil may be used as a future fuel source. Laser-induced fragmentation of these heterocycles in the presence of oxygen could produce a variety of useful gaseous molecules. Unfortunately, these could create a severe pollution problem.⁵

Thietane oxides serve as selective solvents for the separation of hydrocarbons. The extracting power of a mixture of water and thietane 1-oxide is considerably greater than that of dimethyl sulfoxide.¹³

Technological applications have been found for the oxathietane 1,1-dioxides. Ethane β -sultones (19) substituted with long, saturated hydrocarbon chains have been developed as foam-producing surfactants and detergents.¹⁴ Attention is being given to the fluorinated sultones (20), especially by Soviet

⁸ H. Schildknecht, I. Wilz, F. Enzmann, N. Grund, and M. Ziegler, *Angew. Chem., Int. Ed. Engl.* **15**, 242 (1976).

⁹ D. R. Crump, *Tetrahedron Lett.* **52**, 5233 (1978).

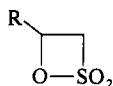
¹⁰ F. S. Abbott, J. E. Coates, and K. Haya, *J. Org. Chem.* **42**, 3502 (1974).

¹¹ C. Leung, *Diss. Abstr. Int. B* **39**, 5938 (1979).

¹² L. Field, W. S. Hanley, P. L. Kelly, W. J. Sanders, J. E. White, I. A. Jaffe, and P. Herryman, *J. Med. Chem.* **16**, 1152 (1973).

¹³ A. P. Zakharov, A. A. Gaile, V. A. Proskuryakov, and L. B. Te, *Zh. Prikl. Khim.* **50**, 152 (1977).

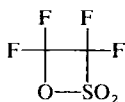
¹⁴ J. K. Weil, A. J. Stirton, and F. D. Smith, *J. Am. Oil Chem. Soc.* **42**, 873 (1965).



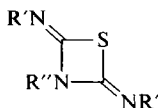
(19) $R = (\text{CH}_2)_{13}\text{CH}_3, (\text{CH}_2)_{15}\text{CH}_3$, etc

research groups. They serve as stabilizers against polymerization of liquid sulfur trioxide.¹⁵

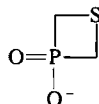
Thiazetidines are investigated with special emphasis on their possible anti-radiation drug activity.¹⁶ Certain 1,3-thiazetidines exhibit pesticidal activity. Compounds **21** are specifically effective as insecticidal and acaricidal agents.¹⁷



(20)



(21)



(22)

Ammonium salts of thiaphosphetanes (**22**) have gained attention as novel pressure and wear resistant lubricants.¹⁸

III. Structural and Physical Properties

Thietanes did not receive very much attention before 1965. But the thietanes now represent by far the most widely researched group of the S-containing four-membered ring systems and, considering all heterocyclic four-membered rings, rank third after the oxetanes and azetidines. The conformational properties of four-membered rings have been elucidated by microwave, IR, Raman, and NMR spectroscopy, electron and X-ray diffraction, and dipole moment measurements. Microwave studies offer an exact picture of molecular dimensions. The theoretical aspects of the stereochemistry of cyclobutane and its heterocyclic analogs, including thietane and its derivatives, have been reviewed by Moriarty.¹⁹

The thietanes and other sulfur-containing analogs exhibit considerable ring strain. The strain energy of thietane itself is 82.4 kJ/mol, about 10 times more than that of the corresponding five-membered thiophene ring.^{20,21}

¹⁵ G. A. Sokol'skij and I. L. Knunjanc, *Izv. Akad. Nauk SSSR, Ser. Khim.* **4**, 873 (1965).

¹⁶ N. Heimer and L. Field, *J. Org. Chem.* **35**, 1668 (1970).

¹⁷ U. Petersen and W. Stendel, Ger. Offen. 2715586 (1978).

¹⁸ A. Schmidt and P. Hamblin, Ger. Offen. 2715529 (1978).

¹⁹ R. M. Moriarty, *Top. Stereochem.* **8**, 273 (1974).

²⁰ B. C. Gilbert, *Chem. Commun.*, 410 (1965).

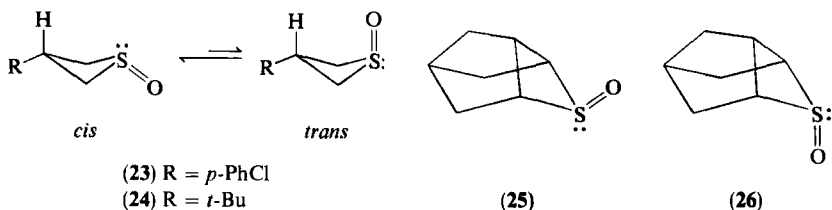
²¹ J. D. Cox, *J. Chem. Phys.* **47**, 5018 (1967).

Far-infrared and microwave studies show that the nonplanar puckered conformation is favored by the thietane ring because of the relatively small C—S—C bond angle and the long C—S bond.^{19,22} The average distance of the C—C bonds is 1.565 Å; the C₂—S bond has a length of 1.89 Å. The average value for other compounds containing the C—S single bond is 1.812 Å.

This phenomenon of bond lengthening seems to be a particular feature of strongly strained rings because other thietane structures exhibit such irregularities as well. The structural configuration and dimensions have been reviewed and described fully by White and Beeson.²³ From microwave data, they calculate the dipole moment of thietane to be 1.85 D.

Microwave spectroscopy is also useful in establishing the O—S—O bond angle for thietane 1,1-dioxides. An angle of 120° could be derived from the special absorption pattern in the 26,500–40,000 cm⁻¹ region.²⁴ By investigating the ring-puckering Raman transitions of its deuterated analogs, Wieser and Kydd contributed to the general conformational picture of the thietane molecule.²⁵

In pioneering work, Johnson and Siegl²⁶ showed that the sulfinyl group of 3-substituted thietane 1-oxides prefers an equatorial position. The significant deshielding effect of the S=O bond on its neighboring equatorial hydrogen atoms (the axial substituents being unaffected) has been useful for the assignment of stereochemical parameters to the four-membered ring sulfoxides.²⁷ 3-Substituted thietane 1-oxides have been shown to have a well-established preference for the axial H atom in the *trans* isomer (**23**) and for the *cis* (diequatorial) geometry (**24**) because of the repulsive interaction between the O and C₃ atoms. Dipole moments for compounds **23** (R = *p*-PhC) and **24** (R = *t*-Bu) in benzene are ~3.22 and 2.80 D, respectively. Valuable models for the study of the deshielding effect of the S=O bond



²² M. Burgers and C. J. Strauss, *J. Chem. Phys.* **47**, 4042 (1967).

²³ M. S. White and E. L. Beeson, *J. Chem. Phys.* **43**, 1838 (1965).

²⁴ W. Ralowski, *Acta Chem. Scand.* **27**, 3128 (1973).

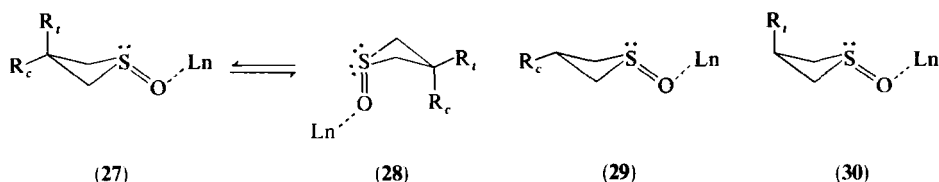
²⁵ H. Wieser and R. A. Kydd, *J. Raman Spectrosc.* **4**, 401 (1976).

²⁶ C. R. Johnson and W. O. Siegl, *J. Am. Chem. Soc.* **91**, 2796 (1969).

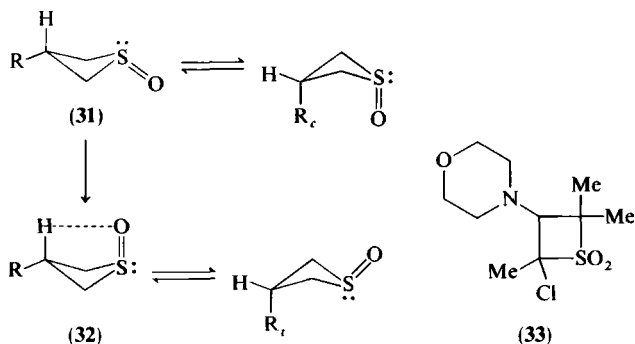
²⁷ W. O. Siegl and C. R. Johnson, *Tetrahedron* **27**, 341 (1971).

are the rigid thietanes **25** and **26**, where only inversion of the sulfoxide is possible.

NMR studies of 3,3-substituted thietane oxides **27** and **28**, involving long range coupling of ring protons, provided added evidence for the folded ring.²⁸ NMR-lanthanide-induced shift (LIS) studies with shift reagents $\text{Eu}(\text{dpm})_3$ or $\text{Yb}(\text{fod})_3$ have provided information about the equilibrium between thietane 1-oxide conformers **29** and **30**.²⁹ The data suggest that the cis-3-substituted thietane 1-oxides exclusively prefer the diequatorial conformation **29** and the corresponding trans isomers **30** favor the equatorial oxygen conformation, at least when bound to the shift reagent.



Dodson *et al.*³⁰ calculated the angle of pucker, using NMR data. Cis-trans preferences of the different conformers of 2,4-diphenylthietanes, its 1-oxide, and 1,1-dioxide were also established. The cis form is preferred by the oxides. In the case of the trans form, the equatorial position of the C=O bond is the preferred arrangement. 3-Substituted 1-oxides were investigated by Siegl and Johnson,³¹ who suggested that the generally preferred positions for the cis groups are equatorial as in **31** but that the axial orientation of the oxygen in the trans isomer **32** is favored because of hydrogen bonding. The conversion of **31** to **32** involves inversion of configuration at the sulfoxide group.



²⁸ W. Wucherpfennig, *Tetrahedron Lett.* **10**, 765 (1970).

²⁹ D. J. H. Smith, J. D. Finlay, C. R. Hall, and J. J. Uebel, *J. Org. Chem.* **44**, 4757 (1979).

³⁰ R. M. Dodson, P. D. Hammen, and R. A. Davis, *J. Org. Chem.* **36**, 2693 (1971).

³¹ W. O. Siegl and C. R. Johnson, *J. Org. Chem.* **35**, 3657 (1970).

Crystallographic measurements have provided additional information about the structure of thietane.³² The ring of 2-(2,6-dimethylphenyl)imino-3,3-dimethyl-4,4-diphenylthietane is puckered, but in the crystal matrix the rings are more likely to be flattened. 2,4-Diphenylthietane 1-oxide molecules are closely packed with their S=O bonds nearly parallel to the ring. No intermolecular hydrogen bonding was observed.³³

X-Ray studies of 2,2-dimethylthietane 1,1-dioxide revealed a nonplanar, rhombic crystal structure without showing any evidence for intra- or intermolecular hydrogen bonding.³⁴

The first thietane 1,1-dioxide to be analyzed by three-dimensional X-ray diffraction was *trans*-4-chloro-3-morpholino-2,2,4-trimethylthietane 1,1-dioxide (**33**),³⁵ which has a monoclinic crystal structure with four molecules occupying a unit cell.

Halogenated thietanes have been studied by Kumakura and Kodoma.³⁶ Unusually large bond moments for the C₂—Cl bond were indicated from dipole moment measurements. X-Ray studies revealed a difference in C₂—S and C₄—S bond lengths, the latter being 0.008 Å shorter than the former.

Exact molecular parameters of oxathietanes and thiazetidines have not been assessed, although the nonplanar puckered-ring structure appears to be the most favorable orientation.³⁷

A conformational analysis of thiacycloalkanes including 2-thiacyclobutane, utilizing molecular mechanics for the calculation of the geometries and energies, was made by Allinger and Hickey.³⁸ The calculated C—C, C—S, C—S—C, C—C—C, and C—C—S bond parameters for the thietane structure, in comparison to those that were derived from electron diffraction, NMR, and microwave measurement, are reported. The experimental and calculated heat of formation of the thiacyclobutane are 14.49 and 14.58 kcal/mol, respectively.

Gas-phase electron diffraction studies on the ring-puckering motion of the thietanes have been carried out by a Japanese group.³⁹ Small-ring geometries in general, including the thietanes and oxathietanes, have been dis-

³² V. Bertolasi and G. Gilli, *Acta Crystallogr., Sect. B*, **B34**, 403 (1978).

³³ G. L. Hardgrove, J. S. Bratholdt, and M. M. Lein, *J. Org. Chem.* **39**, 246 (1974).

³⁴ M. L. Ziegler, J. Weiss, H. Schildknecht, N. Grund, and H. Sasse, *Justus Liebigs Ann. Chem.*, 1702 (1973).

³⁵ G. Andreetti, L. Gavalca, and P. Sgarabotto, *Gazz. Chim. Ital.* **101**, 440 (1971).

³⁶ S. Kumakura, T. Kodoma, *Bull. Chem. Soc. Jpn.* **48**, 2164 (1975).

³⁷ W. Wucherpfennig, *Tetrahedron Lett.* **22**, 1891 (1971).

³⁸ N. L. Allinger and M. J. Hickey, *J. Am. Chem. Soc.* **97**, 5167 (1975).

³⁹ K. Karakida and K. Kuchitsu, *Bull. Chem. Soc. Jpn.* **48**, 1691 (1975).

cussed by Snyder and Carlsen.⁴⁰ A theoretical comparison of the analogous systems thiacyclobutadiene and thiabenzene has been attempted by Bernardi *et al.*⁴¹

IV. Spectroscopic Investigations

A. ULTRAVIOLET-VISIBLE SPECTRA

Ultraviolet-visible spectroscopy has played only a minor role in the investigation of the thietanes and its counterparts. As expected, the colorless compounds absorb in the UV region below 300 nm. For photolysis experiments, many phenylated and alkylated thietanes and thietane oxides have been measured in methyl cyanide or methanol by Langendries and de Schryver.⁴² The spectra exhibit a maximum in the vicinity of 250–265 nm (ϵ 12,000–25,000).

The UV spectra of thiete and its derivatives, measured in 2,2,4-trimethylpentane, show three absorption bands usually located at 215–228 nm (ϵ 1100–2270), 236–248 nm (ϵ 2000–3050), and 285–294 (ϵ 50–567). Thiete itself exhibits these bands at 215 (ϵ 1920), 236 (ϵ 3000), and 285 nm ($\epsilon \sim 50$).⁴³

The UV absorption of several spiro derivatives of thietane such as **34** in methylene chloride had λ_{\max} in the region of 283–287 nm ($\log \epsilon = 1.87$ –2.19).⁴⁴

The naturally occurring thietane acetylene compounds showed in the reduced form three absorption maxima (λ_{\max} 340, 360, and 374 nm) and, in the oxidized form, four bands at 294, 306.5, 393, and 418 nm.⁷

The influence of the d orbitals on the UV-absorption properties of cyclic organic sulfides has been discussed by Williams and Kontuite.⁴⁵

The UV spectra of 1,2-thiazetidinone oxides have been recorded by Beeken and Korte.⁴⁶ Measured in cyclohexane or chloroform, the N-substituted cyclohexyl- (**35**), phenyl-, and aryl-substituted 4,4-bisphenyl-1,2-thiazetidin-3-one 1,1-oxides showed an average absorption band at $\lambda_{\max} = 240$ nm

⁴⁰ J. P. Snyder and L. Carlsen, *J. Am. Chem. Soc.* **99**, 2931 (1977).

⁴¹ F. Bernardi, N. D. Epiotis, S. Shalk, and K. Mislow, *Tetrahedron* **33**, 3061 (1977).

⁴² R. F. Langendries and F. C. de Schryver, *Tetrahedron Lett.* **47**, 4781 (1972).

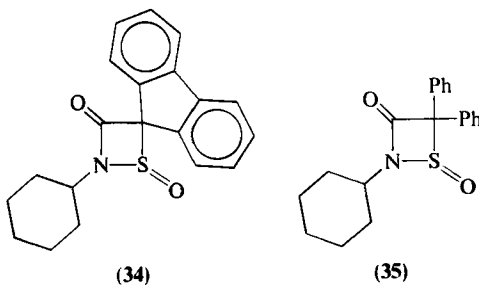
⁴³ D. C. Dittmer, K. Takahashi, and F. A. Davis, *Tetrahedron Lett.* **41**, 4061 (1967).

⁴⁴ G. Seitz and W. D. Mikulla, *Tetrahedron Lett.* **9**, 615 (1970).

⁴⁵ D. R. Williams and C. T. Kontuite, *J. Org. Chem.* **B 2**, 312 (1971).

⁴⁶ H. Beeken and F. Korte, *Tetrahedron* **18**, 1527 (1962).

($\log \epsilon = 3-5$). The nitrophenyl-substituted member, however, exhibited a bathochromic shift to 297 nm.



B. MICROWAVE, INFRARED, AND RAMAN SPECTRA

The IR spectra of *O*-alkyl, phenyl substituted thietanes have been assembled by Ohno *et al.*⁴⁷ The absorption pattern derived from thietanone 1,1-dioxide has been illustrated.⁴⁸

The complete IR spectrum of thiete has been reported by Dittmer *et al.*⁴³ The most characteristic bands of thiete are the C—H stretching vibration at 3165 cm^{-1} and the C=C stretching mode at 1543 cm^{-1} . Thiete derivatives often show the latter absorption band at 1620 cm^{-1} . A collection of IR data on the thiazetidines has been assembled.⁴⁹

The symmetric and asymmetric stretching modes of the SO_2 group in different fused-ring systems containing thietane oxide have been established and discussed.⁵⁰

Extensive investigations into the IR absorption properties of the thiazetidines have been carried out.^{37,51-56} The IR spectra of β -sultones have been analyzed by Truce and Kao Liu.⁵⁷

⁴⁷ A. Ohno, T. Koizuma, and Y. Akasaki, *Bull. Chem. Soc. Jpn.* **47**, 319 (1974).

⁴⁸ R. Langendries, F. C. de Schryver, P. de Mayo, R. A. Marty, and R. J. Schutyser, *J. Am. Chem. Soc.* **96**, 2964 (1974).

⁴⁹ K. Burger and R. Ottlinger, *J. Fluorine Chem.* **11**, 29 (1978).

⁵⁰ H. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.* **10**, 3713 (1969).

⁵¹ W. Ried and O. Möisinger, *Chem. Ber.* **111**, 143 (1978).

⁵² W. Ried and O. Möisinger, *Chem. Ber.* **111**, 155 (1978).

⁵³ Y. Ueno, Y. Masuyama, and M. Okawara, *Tetrahedron Lett.* **30**, 2577 (1974).

⁵⁴ T. Minami, K. Yamataka, Y. Oshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.* **37**, 3810 (1972).

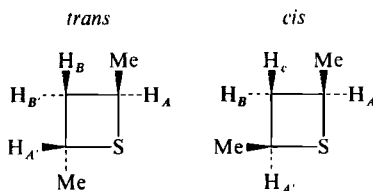
⁵⁵ A. Le Berre and J. Petit, *Tetrahedron Lett.* **3**, 213 (1972).

⁵⁶ E. Schaumann, E. Kausch, and W. Walter, *Chem. Ber.* **110**, 820 (1977).

⁵⁷ W. E. Truce and L. Kao Liu, *Chem. Ind. (London)*, 457 (1969).

C. NUCLEAR MAGNETIC RESONANCE

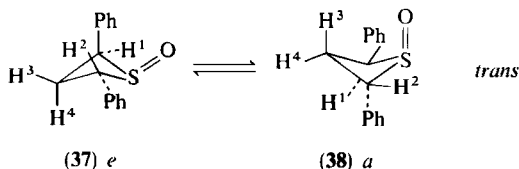
NMR spectroscopy has provided useful information about the stereochemistry of substituted thietanes, the data all being supportive of the non-planar structure. An AA'BC system for the *cis* and an AA'BB' system for the *trans* configurations of 2,4-dimethylthietane (**36**) have been observed.⁵⁸ The 60-MHz spectrum of thietanes, like that of oxetane, has been found to be A₄B₂, the ring-coupling constants not exceeding 1.2 Hz. With the help of an iterative computing program that takes symmetry into account explicitly, Lozach'h and Brailion⁵⁹ have attempted an exact analysis.



(36)

NMR spectroscopy was used to study the course of stereospecific rearrangement of cyclic sulfones to cyclic sulfinates.⁶⁰

The coupling constants of the ring protons have provided useful information about the preferred spatial orientation of two possible conformers. Studies of *trans*-2,4-diphenylthietane 1-oxide (**37**) have shown that the smallest vicinal coupling constant between protons H¹ and H³ amounted to 3.16 Hz. For protons H² and H⁴, $J_{2,4} = 11.90$ Hz, represents the largest vicinal coupling constant. This relationship demonstrates that the molecule with oxygen in the equatorial position (**37**) is favored over the axial conformer (**38**). If both conformers were of equal importance, $J_{1,3}$ and $J_{2,4}$ would have similar values.



The SH⁺ proton of protonated thietane has an absorption at 7.40 ppm, which appears at relatively higher field than its protonated aliphatic counterpart.⁶¹

⁵⁸ L. A. Paquette and J. P. Freeman, *J. Am. Chem. Soc.* **91**, 4320 (1969).

⁵⁹ R. Lozach'h and B. Brailion, *J. Chim. Phys. Phys.-Chim. Biol.* **67**, 340 (1970).

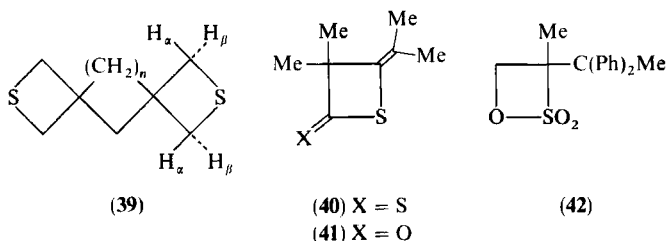
⁶⁰ R. M. Dodson, E. H. Lands, and G. Klose, *J. Org. Chem.* **35**, 2520 (1970).

⁶¹ G. A. Olah and P. I. Szilagyi, *J. Org. Chem.* **36**, 1121 (1971).

The chemical shifts and coupling constants of α -arylated thietanes were determined by Schaal.⁶² In position 4, substituted thietanes show for both the α and β CH₂ groups a multiplet at 3.3–2.7 ppm. The proton in the 4-position shows a triplet at 4.8 ppm. Spectral data for O-, alkyl-, and phenyl-thietanes have been recorded by Ohno *et al.*⁶³

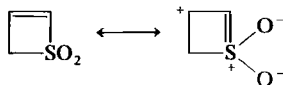
The chemical shift values for substituted *cis* and *trans* thietane *S*-oxides have been obtained by Johnson and Siegl,⁶⁴ and those for fused ring systems by Mazarguil and Lattes.⁵⁰

Dispiro compounds of thietanes **39** show two doublets of a typical AB system centered around 3.2 ppm. The geminal coupling constant of the H _{α} and H _{β} protons is 9.5 Hz.⁴³ NMR spectra of the fully substituted thietanes **40** and **41** are recorded.⁶⁵



NMR studies of thiazetidine derivatives,^{37,51–55,66} β -sultones,⁵⁷ and spiro compounds that contain the thietane structure⁶⁷ have been carried out. With the help of Eu(fod)₃ the AB pair of doublets of sultone **42** could be moved downfield.⁶⁸

Thiete **2** shows a doublet (1H) at δ 6.50, a multiplet (1H) at δ 5.60, and a doublet (2H) at δ 3.80.⁶⁹ In the spectrum of thiete 1,1-dioxide, the signal of the β -olefinic proton is at lower field than that of the α -olefinic proton. The β atom has a lower electron density than the α atom, because of the polarization of electrons in the ring by the sulfone group.



⁶² C. Schaal, *Bull. Soc. Chim. Fr.* **8**, 3064 (1971).

⁶³ A. Ohno, T. Koizumi, and Y. Akasaki, *Bull. Chem. Soc. Jpn.* **47**, 319 (1974).

⁶⁴ C. R. Johnson and W. O. Siegl, *Tetrahedron Lett.* **23**, 1879 (1969).

⁶⁵ E. U. Elam and H. E. Davis, *J. Org. Chem.* **32**, 1562 (1966).

⁶⁶ K. E. Fahrenholz, W. Benz, J. F. Blount, and T. H. Williams, *J. Org. Chem.* **45**, 4219 (1980).

⁶⁷ H. Gotthardt, *Chem. Ber.* **105**, 2008 (1972).

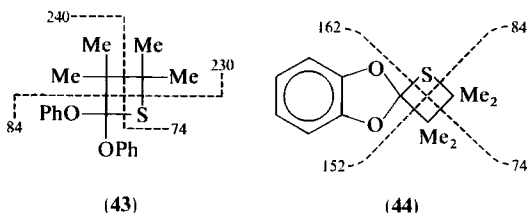
⁶⁸ H. Scott and R. Shilton, *J. C. S. Perkin I*, 247 (1977).

⁶⁹ D. C. Dittmer and M. E. Christy, *J. Org. Chem.* **26**, 1324 (1960).

Proton NMR spectra of the phosphathietanes have been discussed and illustrated along with the ^{13}C -NMR spectrum for thiazetidine derivative **154** and the ^{19}F -NMR spectrum for a fluorinated dithietane ether.⁷⁰

D. MASS SPECTROMETRY

Spectra for most thietanes contain a strong parent ion peak. The four-membered ring is usually fractured into the four possible halves. For example, the cleavage of thietane derivative (**43**) produces peaks at m/e 240, 230, 84, and 74. The parent ion peak is absent at 35°. ⁷¹ Similarly, spirothietane **44** splits to give fragments with m/e 162 (77%), 152 (12%), 84 (100%), and 74 (0.6%). ^{72,73} Decomposition of the thietane nucleus is also characterized by desulfurization and retro 2 + 2 cycloaddition fragments.



The mass spectrometry of four-membered heterocycles has been considerably investigated by Scala and Colon.⁷⁴ Holmes *et al.*⁷⁵ have provided structures associated with metastable ion peaks. The effect of ring size on the fragmentation process of cyclic sulfoxides was studied by Tamagaki and Oae.⁷⁶ Thietane 1-oxide appears as a strong radical ion at m/e 90. At 80 eV no appreciable deoxygenation takes place. Instead, the loss of OH and/or SOH is observed, giving the peak at m/e a value of 73 for $\text{C}_3\text{H}_3\text{S}^+$ and the base peak at m/e 41 for C_3H_5^+ .

Thietane 1,1-dioxide derivatives reportedly produce sulfur dioxide as well as a variety of other fragments. Peaks resulting from retro cycloaddition fragmentation such as CH_2S^+ and CH_2SO_2^+ are never lacking.

⁷⁰ T. Kitazume, *Bull. Chem. Soc. Jpn.* **49**, 2491 (1976).

⁷¹ H. Gotthardt and M. Listl, *Tetrahedron Lett.* **30**, 2849 (1973).

⁷² H. Gotthardt and M. Listl, *Chem. Ber.* **107**, 2552 (1974).

⁷³ H. Gotthardt and M. Listl, *Chem. Ber.* **107**, 1856 (1974).

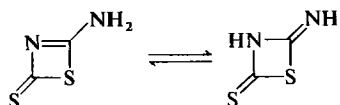
⁷⁴ A. A. Scala and I. Colon, *J. Heterocycl. Chem.* **15**, 421 (1978).

⁷⁵ J. L. Holmes, A. S. Blair, G. M. Weese, A. D. Osborne, and J. K. Terlouw, *Adv. Mass Spectrom.* **7B**, 1227 (1978).

⁷⁶ S. Tamagaki and S. Oae, *Bull. Chem. Soc. Jpn.* **45**, 1767 (1972).

The mass spectrum of thiete **2** contains the parent ion at m/e 72, the base peak at 12 m/e , and fragmentation peaks at 58 for $C_2H_2S^+$, 46 for CH_2S^+ , 45 for CHS^+ , and 39 for $C_3H_3^+$.⁴³

Spectra of thiazetidines have been recorded by Gallow and Klaeser.⁷⁷ The 1,3-thiazete **45** and its tautomer **46** produced the following fragmentation pattern.

	m/e	%
 (45) (46)	SCN HSCN H ₂ SCN H ₂ SCN ₂ CS ₂ H ₂ S ₂ C ₂ N ₂	58 59 69 74 76 118 35 96 100 41 57 59

Fused thiete ring systems produce the thietane cation by ring cleavage. The fragmentation pattern of these products has been established by Dittmer *et al.*⁴³

V. Preparation

A. THIETANES

1. Cycloaddition

The most direct approach to the four-membered S-ring is cycloaddition of sulfenes to alkenes. The sulfenes are generated *in situ* by base-induced dehydrohalogenation of sulfonyl chlorides. Because of their special susceptibility to cycloaddition reactions, research into the chemistry of sulfenes is expanding.

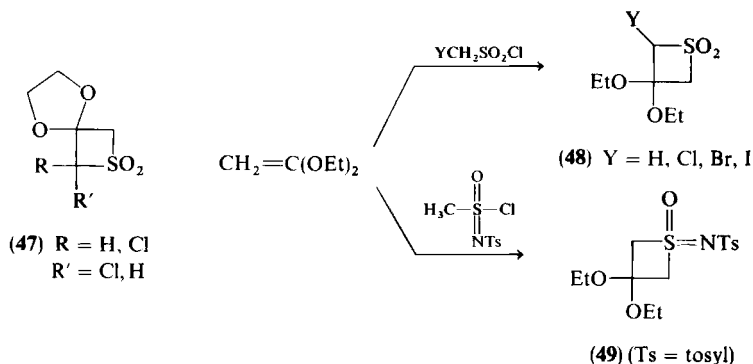
Truce and Norrell noticed in 1963 that sulfenes readily undergo 2 + 2 cycloaddition to ketene diethyl acetal with the formation of 3,3-diethoxythietane 1,1-dioxides.⁷⁸ The same reaction was carried out by Paquette, using 1,1-dioxide ketals with cyclic α -halo sulfones in which the corresponding chloroketal derivatives **47** were formed.⁷⁹ This approach may be illustrated by the addition of ketene diethyl acetal to halogenated sulfenes⁸⁰ and to

⁷⁷ G. Gallow and K. Klaeser, *Z. Anorg. Allg. Chem.* **434**, 112 (1976).

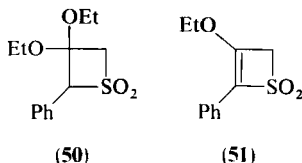
⁷⁸ W. E. Truce and J. R. Norrel, *J. Am. Chem. Soc.* **85**, 3236 (1963).

⁷⁹ L. A. Paquette, *J. Am. Chem. Soc.* **93**, 944 (1971).

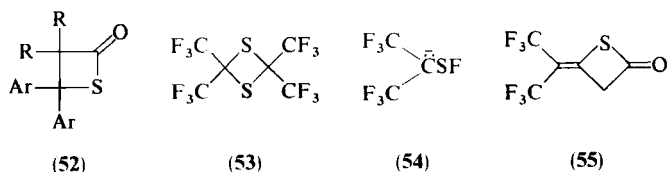
⁸⁰ W. Ried and J. Paraskevova, *Sulfur Lett.* **1**, 79 (1982).



halogenated sulfinimines,⁸¹ giving the products **48** and **49**, respectively. Reaction of benzylsulfonyl chloride with ketene diethyl acetal also leads directly to the cyclic derivatives **50** and **51**, the active intermediate being the sulfene.⁸² However, benzoylsulfonyl fluoride does not react under comparable conditions.



Many cycloaddition reactions have been carried out with ketenes and thioketones.⁸³ The products are thiolactones (**52**). Hexafluorothioacetone and diphenylketene, however, do not undergo cycloaddition even after prolonged heating at 100°C. Good results can be obtained when the more stable dimer of this fluorinated thioketone (**53**) is used. Anionic monomer **54** could be released by the action of potassium fluoride in an aprotic solvent.⁸⁴ Two-step cycloaddition to diphenylketene yields ketone **55**.



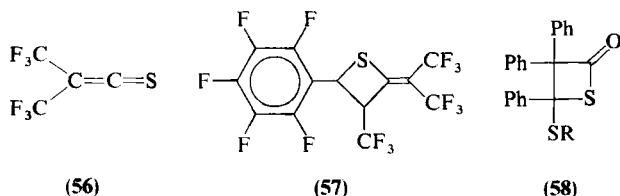
⁸¹ C. R. Johnson and E. U. Johnson, *J. Am. Chem. Soc.* **92**, 3815 (1970).

⁸² Y. Shiroto, T. Nagai, and N. Tokura, *Tetrahedron Lett.* **19**, 2343 (1968).

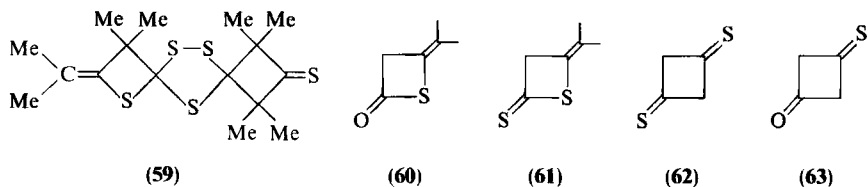
⁸³ H. Kohn, P. Charumilind, and Y. Gopichard, *J. Org. Chem.* **43**, 4961 (1978).

⁸⁴ Z. Zubovics and N. Ishikawa, *J. Fluorine Chem.* **8**, 43 (1976).

Cycloaddition may be varied by the use of fluorinated thioketenes in place of ketenes.⁸⁵ Olefins and Schiff bases serve as the other component. Thus thioketene **56** cycloadds to a Schiff base to give product **57** in a 79% yield.⁸⁶ In a further variation, reaction of dithiobenzoate esters with diphenylketene yields 61% of product **58**.⁸⁷



An interesting spiro compound (**59**) that contains the thietane ring was obtained in minor amounts by dimerization of dimethylketene and subsequent treatment with P_2S_5 .⁶⁵ Pyrolysis of the spiro structure produced **60** and the thietanethione **61**, which can also be prepared by base-catalyzed rearrangement of **62**, a process that can be carried out as well with **63** to give the 2-thietanone **60**. The solvent and the basicity of the catalyst are important parameters in this rearrangement.



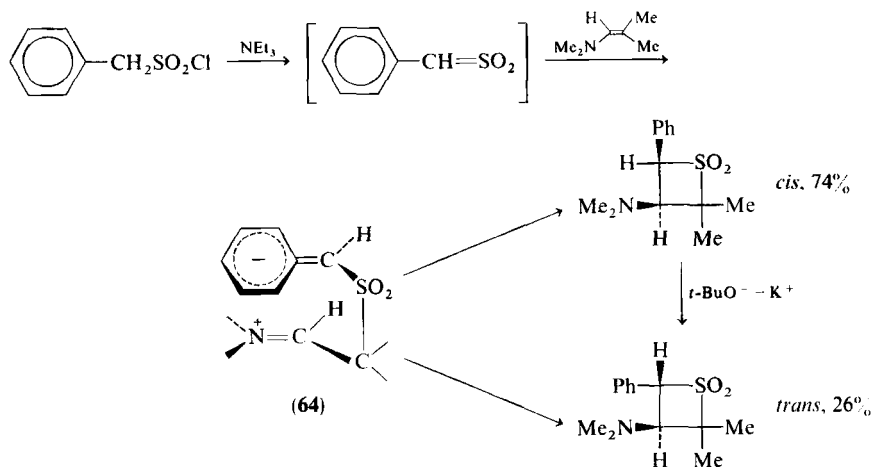
One of the most widely applied cycloaddition techniques for the preparation of thietanes is the reaction of sulfenes with enamines. The stereochemistry of these reactions has been extensively investigated by Truce and Rach.⁸⁸ Whether the mechanism is a two-step or a concerted process, both in accordance with the stereoselective formation of the *cis* form in Scheme 1, is still unresolved. The special orientation of the 1,4-dipolar intermediate **64**, in which the charged phenyl and dimethylamino moieties are in proximity, enforces the *cis* geometry of the resulting thietane dioxide. In the concerted mode of reaction, formation of the orthogonal oriented unsaturated system, **65** should also yield the *cis* cycloadduct.

⁸⁵ M. S. Raasch, *J. Org. Chem.* **35**, 3478 (1970).

⁸⁶ M. S. Raasch, *J. Org. Chem.* **43**, 2500 (1978).

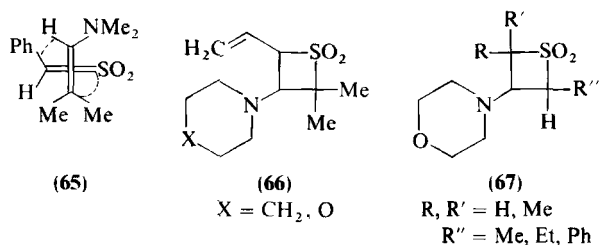
⁸⁷ V. N. Drozd and O. A. Popova, *Zh. Org. Khim.* **15**, 2602 (1979).

⁸⁸ W. E. Truce and J. F. Rach, *J. Org. Chem.* **39**, 1109 (1974).



SCHEME 1

The stereochemistry of sulfene-enamine cycloaddition has also been followed by Drozd *et al.*,⁸⁹ who studied the method of asymmetric induction in the preparation of compounds **66** and **67**.

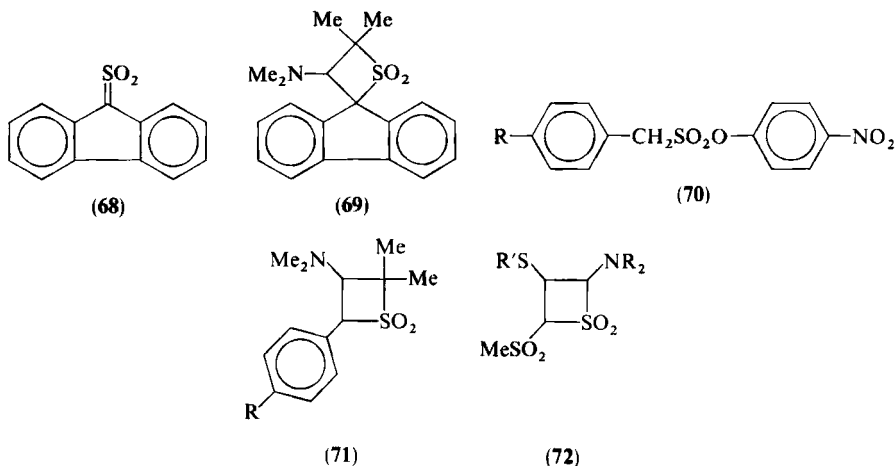


The stereoselective or stereospecific formation of these compounds and their interaction with butyllithium was studied with the help of NMR. Paquette and Freeman first applied asymmetric induction to the synthesis of four-membered rings,⁹⁰ especially with the sulfene-enamine 2 + 2 cycloaddition. The *in situ* generation of sulfene **68** by dehydrochlorination with butyllithium of the sulfonyl chloride allowed the formation of cycloadduct **69** in 88% yield. In a variation, the sulfene may be generated by base-induced

⁸⁹ V. N. Drozd, and V. V. Sergeichuk, and N. D. Antonova, *Zh. Org. Khim.* **40**, 1498 (1974).

⁹⁰ L. A. Paquette and J. P. Freeman, *J. Am. Chem. Soc.* **91**, 7548 (1969).

elimination of phenol from a phenylsulfonate ester (70). In this way treatment of enamines with sulfonate esters in the presence of *tert*-butylpotassium in tetrahydrofuran gives thietane 71.⁹¹⁻⁹³



Simple unsaturated sulfides cannot be used in place of enamines in cycloaddition reactions with sulfines leading to thietane dioxide derivatives.⁹⁴ Alkyl, vinyl, and cycloalkylvinyl sulfides, which carry a C=C double bond, are considerably less nucleophilic than the enamines and thus do not partake in cycloadditions to sulfene. But when the more electrophilic methylsulfonyl sulfene is used in association with an unsaturated sulfide substituted with a strong electron donating alkylamino group, the formation of thietane dioxides 72 is successful.

Good yields for the 3-aminothietane 1,1-dioxides can be expected by the reaction of phenylmethanesulfonyl chloride with *trans*- β -dimethylamino-styrene in the presence of triethylamine.¹⁰ Reaction proceeds by the pathway given in Scheme 1.

The reaction of *N,N*-dimethyl-(*E*)-styrylamine (73) with a halogen-substituted methanesulfonyl chloride allowed the first stereoselective formation of the halogenated thietane 1,1-dioxide 74, which then could be converted to the corresponding thiete sulfone 75 via a Cope elimination of the corresponding *N*-oxide.⁹⁵

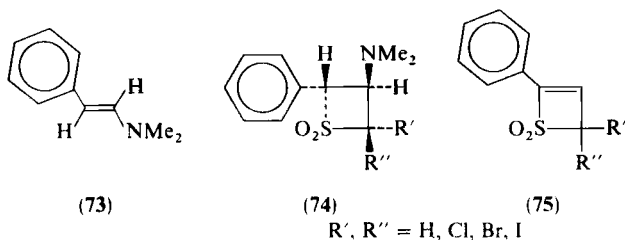
⁹¹ A. W. Bogatskij and T. I. Dawidenko, *Zh. Org. Khim.* **7**, 1548 (1971).

⁹² V. N. Drozd, V. V. Sergeichuk, and V. A. Moskalenko, *Zh. Org. Khim.* **11**, 135 (1975).

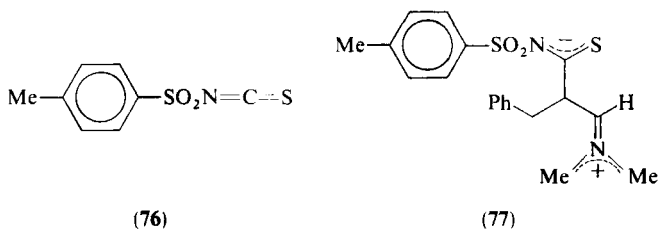
⁹³ V. N. Drozd and V. V. Sergeichuk, *Zh. Org. Khim.* **11**, 1317 (1975).

⁹⁴ E. N. Prilezhaeva, N. P. Petukhova, V. I. Kurilkin, A. U. Stepanyants, and V. P. Lezina, *Izv. Akad. Nauk SSSR, Ser. Khim.* **8**, 1827 (1974).

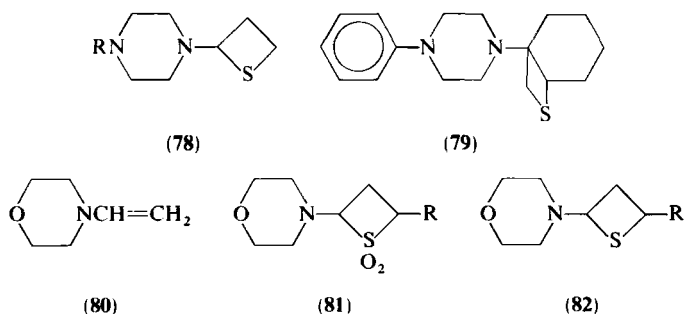
⁹⁵ W. Ried and H. Bopp, *Chem. Ber.* **111**, 1527 (1978).



Cycloaddition reactions of sulfonyl isothiocyanate **76** and β,β -disubstituted enamines were studied by Schaumann *et al.*⁹⁶ The mechanism of cycloaddition is postulated to consist of two steps, originating with the formation of the zwitterionic adduct **77**.



Application of the enamine-sulfene cycloaddition allowed the synthesis of **78** and **79** from the corresponding α,β -unsaturated amines and sulfenes. Similarly, using enamine **80**, the crystalline morpholino thietane dioxides (**81**) were produced.⁴⁹ Elimination via the *N*-oxide gave the corresponding thiete dioxide, whereas reduction by LiAlH_4 yielded the thietane **82**.

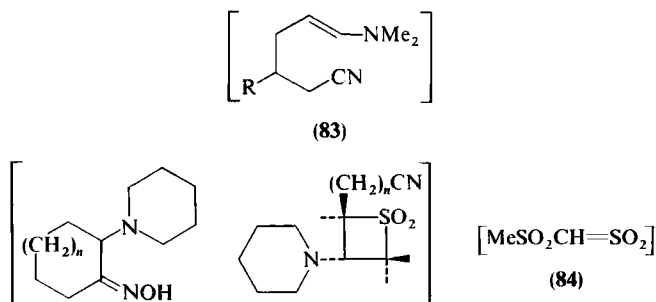


An interesting variation to cycloadditions involving sulfenes is a reaction carried out with α -amino ketoximes, by which thietane dioxides are produced.⁹⁷ The authors suggested a two-step mechanism via the intermediate cyanoenamine **83**. Higher yields were obtained when the oximes were

⁹⁶ E. Schaumann, S. Sieveking, and W. Walter, *Tetrahedron* **30**, 4147 (1974).

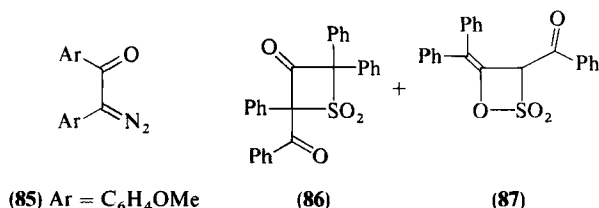
⁹⁷ S. C. Chen and Y. L. Chow, *Can. J. Chem.* **52**, 2283 (1974).

treated with phenylmethanesulfonyl chloride because of the facile generation of phenylsulfene.

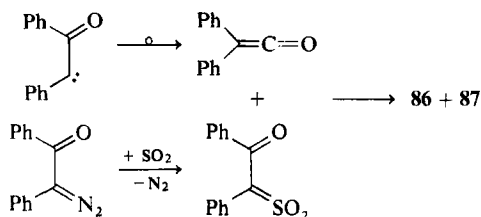


Cycloaddition of sulfenes to α,β -unsaturated sulfides that contain electron-donor substituents, such as alkyl and arylthio groups, has proved to be a valuable synthetic pathway for the production of thietane 1,1-dioxides. Methylsulfonylsulfene (**84**) is more reactive than the regular sulfenes because of the activating effect by the strong electron-acceptor properties of the sulfonyl group. If, in addition, a strong electron-donor group, such as the alkylamino function, is provided by the unsaturated sulfide molecule, the cycloaddition proceeds much more readily.

Azibenzils **85** are effective reagents in the synthesis of 2-thietanones. With thiobenzophenone, elimination of nitrogen produces, via intramolecular cyclization, four- and five-membered ring isomers.⁹⁸



Direct sulfination of azibenzils in benzene yields cycloadducts **86** and **87**. The diazoketones thermally decompose and easily undergo partial Wolff

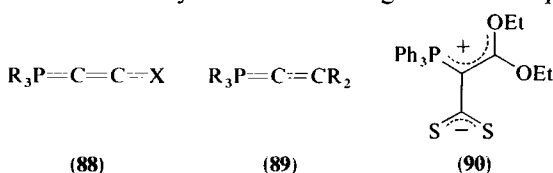


SCHEME 2

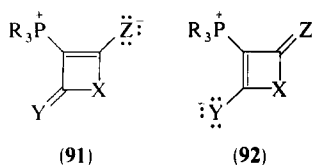
⁹⁸ S. Mataka, S. Ishii, and M. Tashiro, *J. Org. Chem.* **43**, 3730 (1978).

rearrangements to give ketenes. The actual cycloaddition then takes place between the ketene and the ketosulfone (Scheme 2).⁹⁹

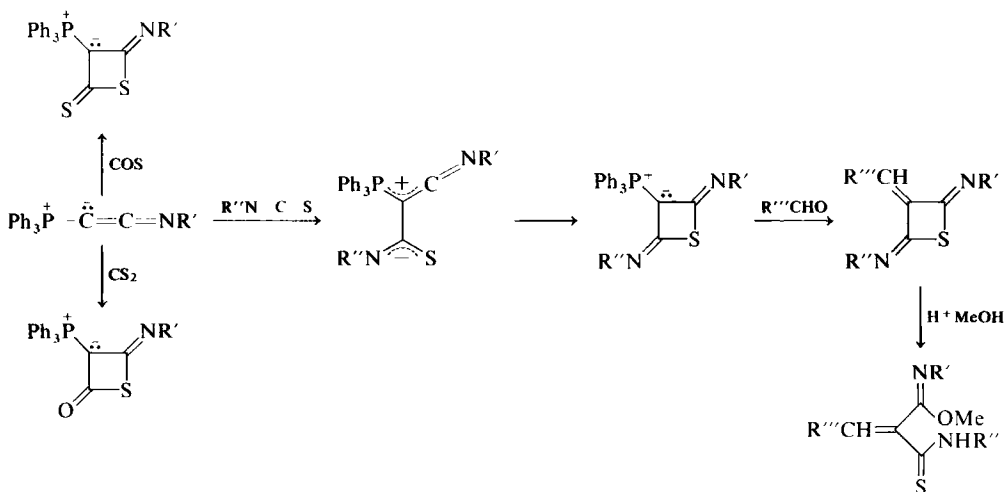
Bestmann established a useful method for the preparation of thietanes by cycloaddition of heteroallenes with phosphaaallene ylides **88** or phosphacumulene ylides (**89**).¹⁰⁰ Because of the strong nucleophilic character of the sulfur atom, 1,4-cyclization via the intermediate **90** takes place. The polarization of the C=S bond may exert a stabilizing effect on the positive charge



of the transition states, from which retrocyclization is possible via electrophilic ring-opening reactions. Cycloconversion to the ring systems **91** and **92** is possible by exchange of the exocyclic substituent X against heteroatom



Z. The possible compounds that can be obtained from the cumulenes and S-containing allenes are outlined in Scheme 3.

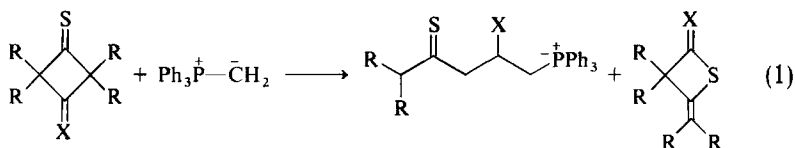


SCHEME 3

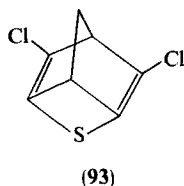
⁹⁹ T. Nagai, M. Tanaka, and N. Tokura, *Tetrahedron Lett.* **60**, 6293 (1968).

¹⁰⁰ H. J. Bestmann, *Angew. Chem., Int. Engl. Ed.* **16**, 349 (1977).

With no major research on the reaction of phosphorus ylides and aliphatic or alicyclic thiones prior to their investigation, Krapcho *et al.*¹⁰¹ were able to elaborate a useful method for the synthesis of the thietane ring system in addition to the preparation of novel types of thiocarbonyl stabilized ylides (Eq. 1).



A unique reaction for the preparation of a fused cyclic system containing the thietane ring is the addition of sulfur dichloride to norbornadiene to give **93**.¹⁰² This reaction, however, failed to produce similar results with other cyclic 1,4-dienes.



Radical intramolecular cyclization of ethylene mercaptans leads to thiophene as well as thietane derivatives.¹⁰³

2. Photocycloaddition

Photocycloaddition of thiones to alkenes is the most popular and fruitful method for the preparation of the thietane system. In analogy to the formation of the oxetanes by cycloaddition of the electronic excited $^3(n,\pi^*)$ carbonyls, thietanes can be expected to arise photochemically from aromatic thioketones and substituted olefins as well as 1,2- and 1,3-dienes.^{104,105}

Thiobenzophenone serves as a source of a sulfur atom and, because of its blue color, which disappears on photocycloaddition, permits exact control over the reaction time. A mixture of thiobenzophenone and α -phellandrene must be irradiated for 70 hr before the blue color disappears (Eq. 2)¹⁰⁶ and

¹⁰¹ A. P. Krapcho, M. P. Silvon, and S. D. Flanders, *Tetrahedron Lett.* **43**, 3817 (1974).

¹⁰² B. M. Trost and W. L. Schinski, *J. Am. Chem. Soc.* **93**, 676 (1971).

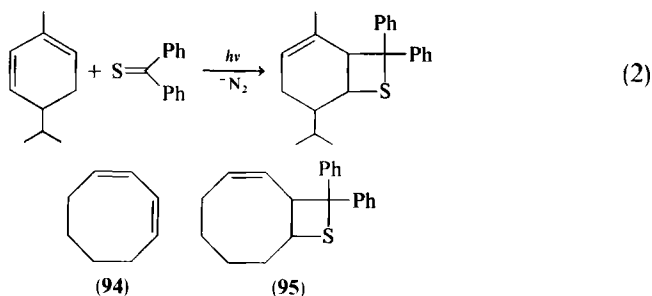
¹⁰³ J. M. Surzur, C. Dupny, M. P. Crozet, and N. Aimar, *C. R. Acad. Sci., Ser. C* **369**, 849 (1969).

¹⁰⁴ A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *J. Am. Chem. Soc.* **91**, 5038 (1969).

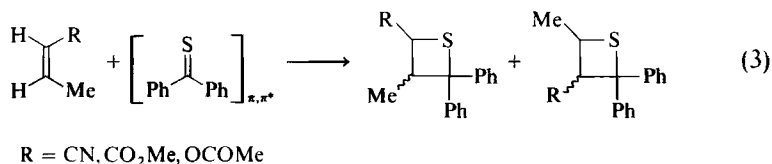
¹⁰⁵ G. Tsuchihashi, H. Yamauchi, and M. Fukuyama, *Tetrahedron Lett.*, 1971 (1967).

¹⁰⁶ Y. Omote, M. Yoshida, K. Yoshioka, and N. Sugiyama, *J. Org. Chem.* **32**, 3676 (1967).

82 hr of irradiation are necessary for cyclooctadiene (94) and thiobenzophenone to give the fused thietane derivative 95.¹⁰⁷ The reaction gave optimal yields at room temperature; heating to 100°C did not give the desired thietane product.



Electron-rich and electron-poor olefins influence the outcome of the thietane reaction. Olefins containing electron-withdrawing groups react only with the π, π^* state of the thiones to produce the four-membered S-ring (Eq. 3).^{64, 108-110} The mechanism is described as an electron transfer from



the π orbital of the π, π^* state of the thiobenzophenone to the antibonding orbital of the electron-deficient double bond of the olefin. But olefins that contain an electron-releasing group are only reactive with the n, π^* triplet state of the thioketone and 1,4-dithiolanes (Scheme 4). The intermediate diradical can either produce the thietane ring by combining the radical centers or react with another thione molecule to give the dithiolane ring.

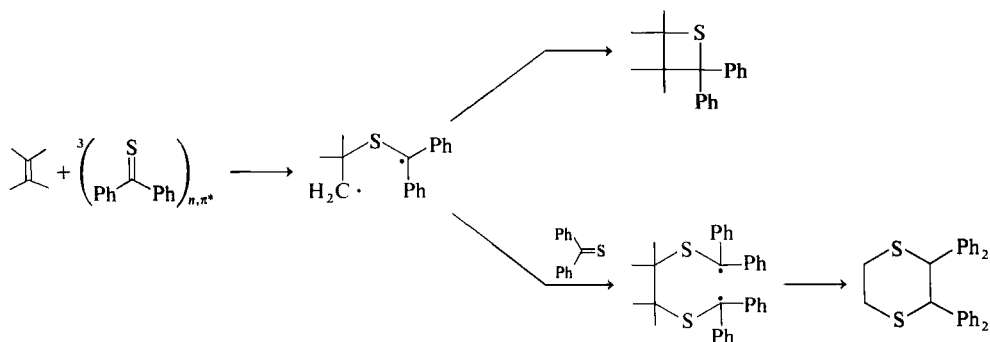
With electron-rich olefins, the rate of addition to a second thione is faster than that of the combination of the intermediate diradical to thietane. By substituting these olefins, however, with groups that provide steric hindrance, the reaction of the diradical with another thione molecule can be inhibited. Irradiation of thiobenzophenone and 1,3-cyclooctadiene, propenylbenzene,

¹⁰⁷ K. Yamada, M. Yoshioka, and N. Sugiyama, *J. Org. Chem.* **33**, 1240 (1968).

¹⁰⁸ A. Ohno, Y. Ohnishi, M. Fukuyama, and G. Tsuchihashi, *Tetrahedron Lett.* **3**, 161 (1969).

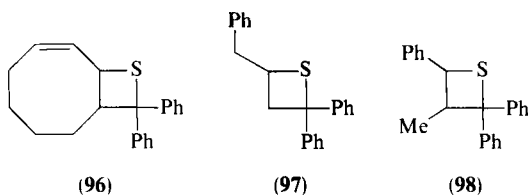
¹⁰⁹ A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *Tetrahedron Lett.* **4**, 283 (1969).

¹¹⁰ A. Ohno, T. Koizumi, and Y. Akasaki, *Bull. Chem. Soc. Jpn.* **47**, 319 (1974).

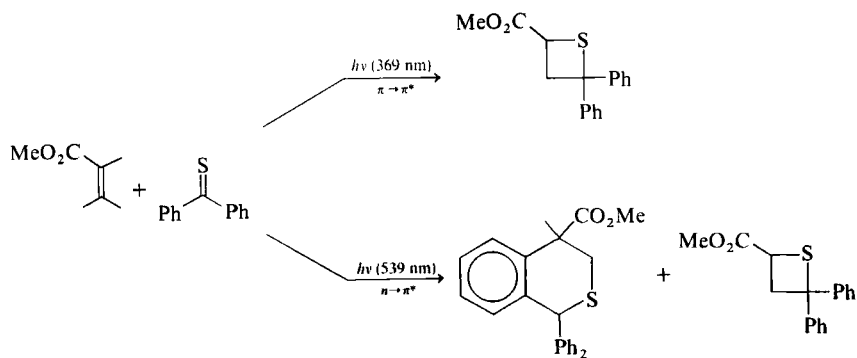


SCHEME 4

or methylstyrene with 589-nm light that excites the n,π^* transition affords good yields of the thietane derivatives **96**, **97**, and **98**, respectively.



Gotthardt, however, showed that by lowering the thione concentration the thietane–dithiolane yield ratio could be systematically directed to favor the four-membered heterocycle. A low thione concentration inhibits addition of the intermediate diradical to another thiophenone molecule to produce the dithiane^{67,111,112} (Scheme 5).

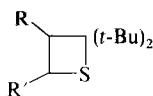
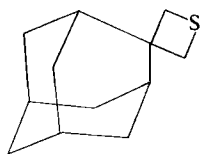


SCHEME 5

¹¹¹ H. Gotthardt, *Chem. Ber.* **107**, 2544 (1974).

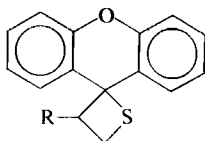
¹¹² H. Gotthardt, *Chem. Ber.* **107**, 2552 (1974).

Thietane is often the main product when thioketones are excited to a higher state (S_2) in activated olefinic solvents (π, π^*). In nonactivated olefinic solvents, however, H abstraction is the favored reaction as opposed to cycloaddition. Rajee and Ramamurthy¹¹³ observed a competition between addition to the double bond and an allylic proton abstraction by the thioketone. The formation of thietanes from electron-rich as well as electron-poor olefins is stereospecific but not regiospecific. Di-*tert*-butylthione and adamantthione are similar in their behavior toward proton donors and olefins. They undergo cycloaddition to both electron-rich and -poor olefins from both higher (S_2) and lower states. Thiobenzophenone and xanthione partake in photocycloadditions to electron-poor olefins only from the higher states (S_2) and to electron-rich olefins only from the lower states (T_1).

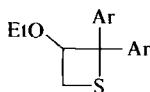



R, R' = H, OEt, Me, Et, CN

Irradiation of thiones with 589-nm light in the presence of electron-deficient olefins produced **99** and **100**. By-product **89** is the result of an ortho attack on the benzene ring.

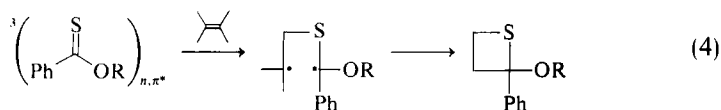


(99) R = Ph, CO₂Me



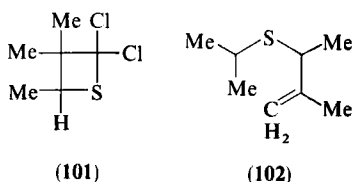
(100) Ar = -OMe

Studies with other thiocarbonyl compounds reveal a different reactivity pattern from that of thiones in the presence of olefins. *O*-Alkyl thiobenzoates do not form dithiane products. Instead, if an olefin carries no bulky substituents, the intermediate diradical cyclizes directly to the thietane ring⁶³ (Eq. 4). The excited $^3(n, \pi^*)$ state of thiophosgene reacts with alkenes to

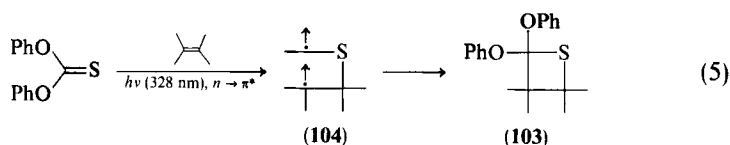


¹¹³ R. Rajee and V. Ramamurthy, *Tetrahedron Lett.* **37**, 3463 (1978).

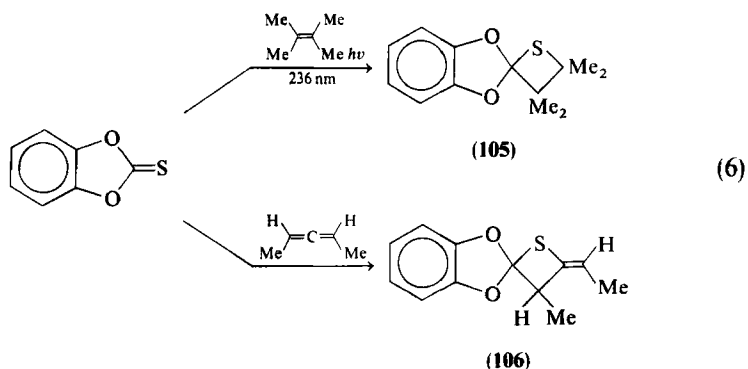
produce the chlorinated thietanes **101**, which are highly sensitive to hydrolysis.^{71,114} Spin inversion of a diradical triplet intermediate having two tertiary radical centers can lead via intramolecular hydrogen-atom transfer to an acyclic structure (**102**).



Selective excitation of the $^1(n,\pi^*)$ state of diphenylthiocarbonate resulted in the formation of the corresponding thietanes **103**^{72,73} (Eq. 5). The 2 + 2 cycloaddition proceeds via intermediate **104** and is regiospecific.



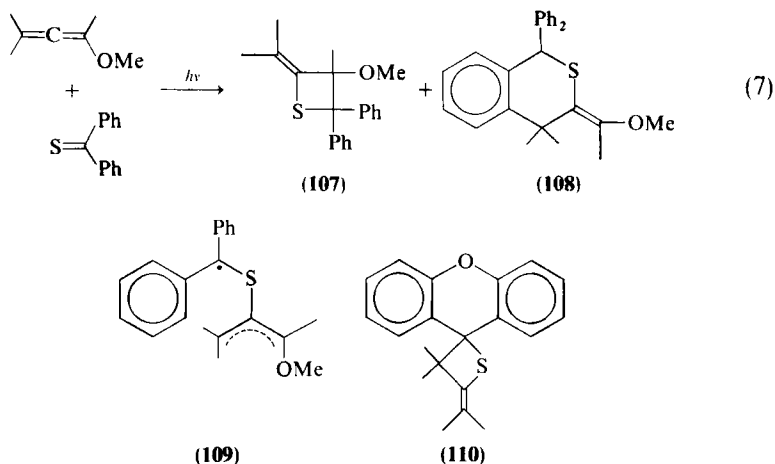
The spiro photocycloadducts **105** and **106** were produced in moderate yields by irradiation of a thiocarbonate (Eq. 6). The photocycloaddition of



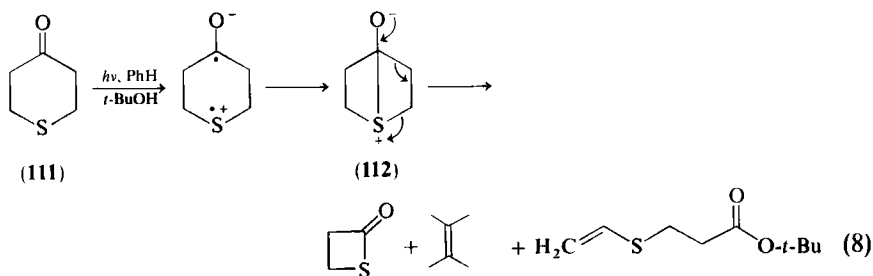
aromatic thiones to allenes, studied by Bos *et al.*,¹¹⁵ gives thietane **107** and isomer **108** (Eq. 7). Cyclization of the postulated diradical **109** can lead to **107** or **108**. In the case of the more rigid xanthene-9-thione, ortho attack on the benzene ring is not favored so that thietane **110** is the only photoadduct.

¹¹⁴ H. Gotthardt, *Tetrahedron Lett.* **15**, 1221 (1973).

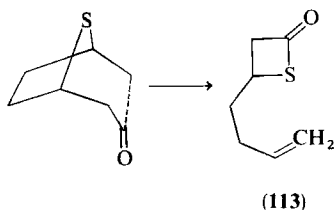
¹¹⁵ H. J. T. Bos, H. Schnikel, and T. C. M. Wijsmann, *Tetrahedron Lett.* **42**, 3905 (1971).



Ring closure was observed by Johnson and Berchtold, who irradiated cyclic γ -ketosulfide **111** and *tert*-butyl alcohol with 253.7-nm light. A 2-thietanone derivative¹¹⁶ was formed following intramolecular electron transfer from the sulfur atom to the excited carbonyl. An unstable dipolar

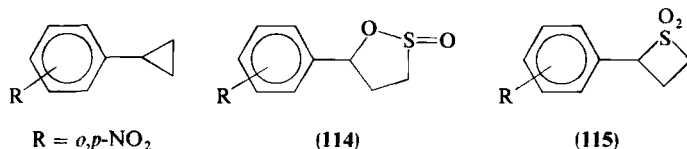


molecule (**112**) is produced, which decomposes to thietanone and olefin fragments (Eq. 8). Similarly, **113** was obtained; the reaction was carried out in Freon.¹¹³



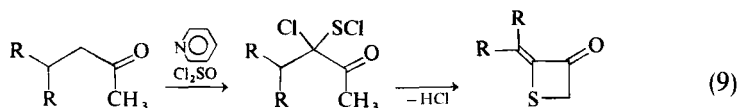
¹¹⁶ P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.* **35**, 584 (1970).

Photochemical addition of SO_2 to arylcyclopropanes have reportedly produced the two isomers **114** and **115**.¹¹⁷

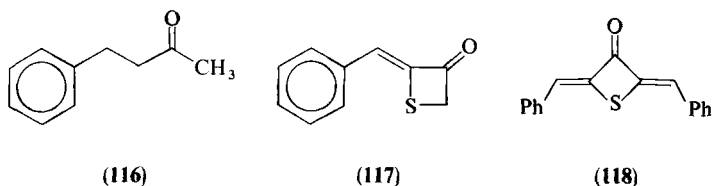


3. Eliminative Cyclization

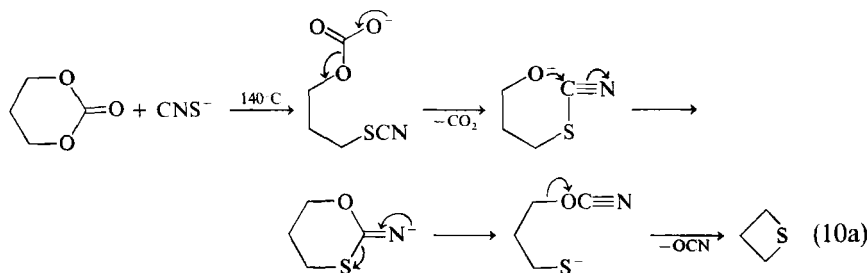
Thionyl chloride undergoes a cyclization reaction with ketones.¹¹⁸ Enolization of the intermediate sulfenyl chloride, followed by the base-induced intramolecular nucleophilic displacement reaction, produces the thietanone



(Eq. 9). The same synthetic method applied to the ketone **116** gave the 3-thietanone **117** which could be derivatized to **118**.



The thermal condensation of a cyclic carbonate with potassium thiocyanate represents a practical method for the synthesis of the four-membered S-ring system (Eq. 10a).¹¹⁹

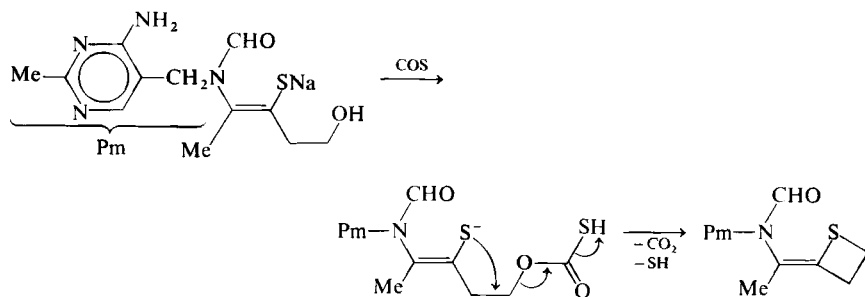


¹¹⁷ D. E. Applequist and L. F. McKenzie, *J. Org. Chem.* **42**, 1251 (1971).

¹¹⁸ A. J. Krubsack, T. Higa, and W. E. Slack, *J. Am. Chem. Soc.* **92**, 5258 (1970).

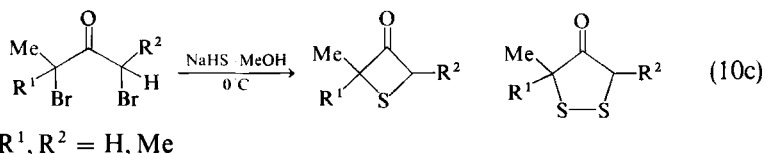
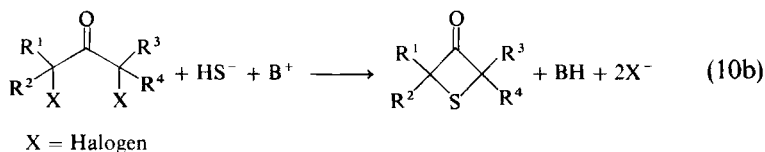
¹¹⁹ S. Searles and E. F. Lutz, *J. Am. Chem. Soc.* **80**, 3168 (1958).

Thietanes have been obtained from thiamine derivatives and carbonyl sulfide.¹²⁰ (Scheme 6).



SCHEME 6

The most effective synthesis for thietanones is the eliminative cyclization of halogenated ketones with hydrogen sulfide ions in the presence of bases (Eq. 10b).¹²¹ The reaction of 1,3-dibromoketone derivatives with sodium hydrogen sulfide produced 3-thietanones in association with a five-membered cyclic disulfide (Eq. 10c).¹²²

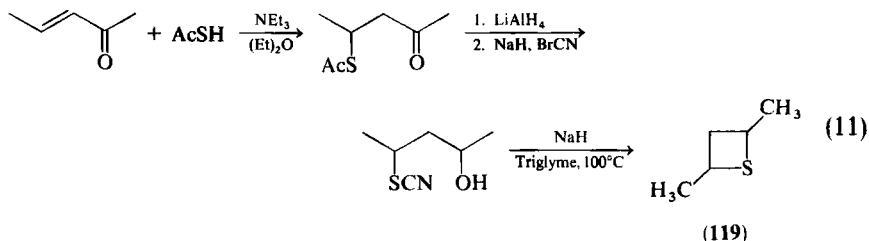


The yields of thietanone depend on the number of methyl groups attached to the 1,3-dihaloketones, a relationship attributed to the "gem effect." Thus the unsubstituted thietane failed to form. Thietanes have been synthesized by a series of reactions involving addition of thiolacetic acid to a vinyl ketone, reduction with LiAlH₄, substitution of the acyl group by the nitrile function, and subsequent ring closure to a cis-trans mixture of **119** (Eq. 11).

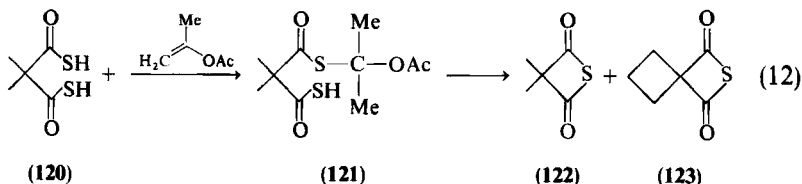
¹²⁰ A. Takamizawa, K. Hirai, and T. Ishiba, *Tetrahedron Lett.* **6**, 441 (1970).

¹²¹ B. Föhlisch and W. Gottstein, *Justus Liebigs Ann. Chem.* **11**, 1768 (1979).

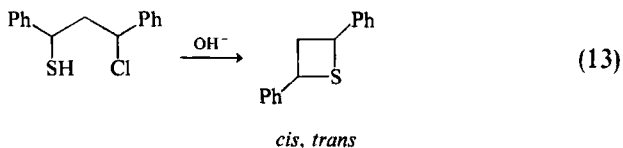
¹²² B. M. Trost, R. W. LaRochelle, and R. C. Atkins, *J. Am. Chem. Soc.* **91**, 4320, and 2175, 2177 (1969).



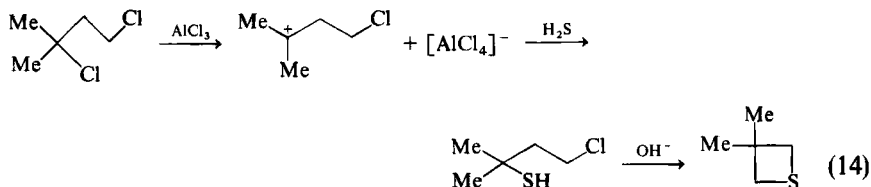
Dimethylbisthiomalonic acid (**120**), when treated with an acylated enol, produced intermediate **121**; thietanediones **122** and **123** then were formed by elimination of thioketone and acetic acid (see Eq. 12).¹²³ Similarly, cyclobutane-1,1-bisthiolcarboxylic acid gave **123**, a previously unknown sulfur analog of malonic anhydride, (Eq. 12). Thermolysis of **120** also results in the formation of the four-membered heterocycles in addition to carbonyl sulfide, hydrogen sulfide, and thiocarbonic acid.⁵⁹



Ring closure to the *cis*-*trans* isomers of the thietanes can be achieved by intramolecular dehydrohalogenation of 1,3-substituted chlorothiols (Eq. 13).



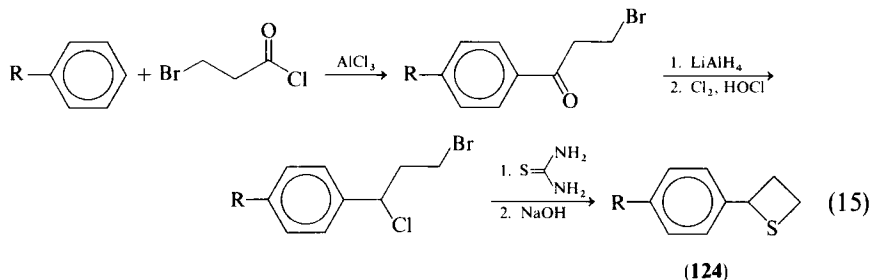
The synthesis of 2,2-dimethylthietane—the malodorous anal secretion of the mink—includes a 1,4-elimination of a suitably substituted chlorothiols, which was prepared from 1,3-dichloro-3-methylbutane¹²⁴ (Eq. 14).



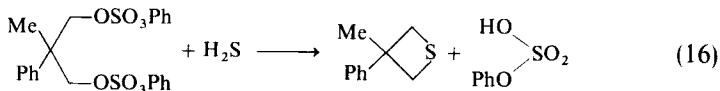
¹²³ J. H. Schauble, W. A. Vansaun, and J. D. Williams, *J. Org. Chem.* **39**, 2946 (1974).

¹²⁴ C. Mayer, *Helv. Chim. Acta* **57**, 272 (1974).

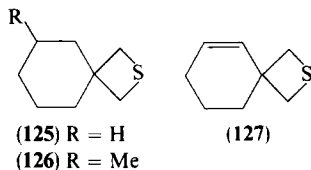
A new approach to the formation of the 2-aryl thietane derivatives **124** includes Friedel–Crafts acylation to give a β -halo ketone. Following conversion of the ketone to the chloride, cyclization is effected with thiourea^{125,126} (Eq. 15).



The 2-substituted derivatives of the thietanes have received considerable attention in recent years. In contrast, 3-substituted members have been neglected. 3-Alkyl-3-arylthietanes were not synthesized prior to the work of Buza *et al.*,¹²⁷ who first prepared 3-methyl-3-phenylthietanes and their oxides. The mode of ring closure consisted in the condensation of 1,3-disulfonate esters with hydrogen sulfide (Eq. 16). Other compounds derived



by this method include spirothietanes such as **125**, **126**, and **127**.



4. Ring Expansion or Contraction of Other Heterocycles

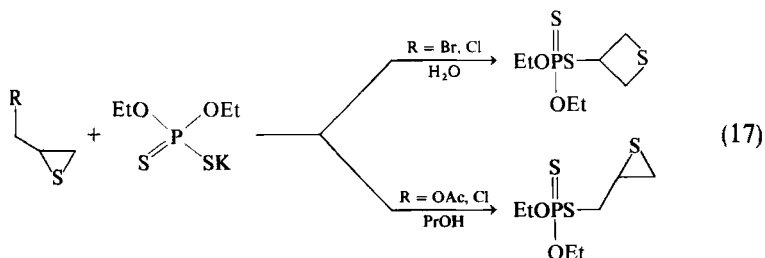
α -Substituted thioepoxides may give a thietane when treated with potassium diethylthiophosphate¹²⁸ (Eq. 17). The competition between ring expansion and side-chain substitution is markedly influenced by the nature of the substituent R and the solvent.

¹²⁵ C. Schaal, *C. R. Acad. Sci., Ser. C* **271**, 1015 (1970).

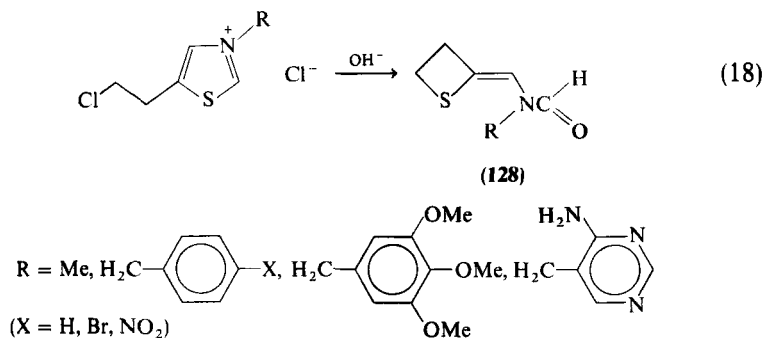
¹²⁶ C. Schaal, *Bull. Soc. Chim. Fr.* **8**, 3064 (1971).

¹²⁷ M. Buza, K. K. Andersen, and M. D. Pazdon, *J. Org. Chem.* **43**, 3827 (1978).

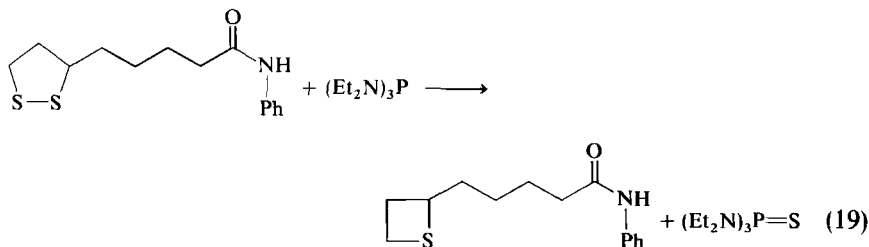
¹²⁸ O. N. Nuretdinova and F. F. Guseva, *Izv. Akad. Nauk SSSR. Ser. Khim.* **8**, 1910 (1970).



Base-induced rearrangement of quaternized thiazoles results in the formation of formamido-methylene thietanes (**128**) (Eq. 18).



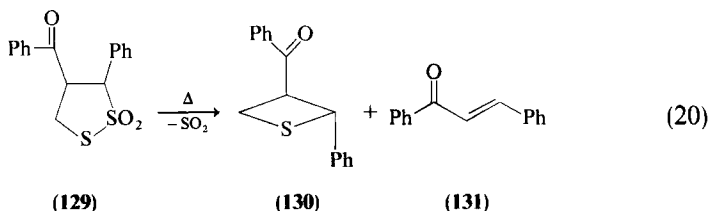
An interesting synthetic approach to thietanes is the selective desulfurization of cyclic disulfides.¹²⁹ The treatment of dithiolanes with a diethylaminophosphine results in a ring contraction to thietanes, (Eq. 19). This has been demonstrated with α -lipoic acid, a coenzyme with a dithiolane structure involved in the biological oxidation of pyruvic acid. The reaction is proposed to be initiated by the electrophilic attack of the phosphorus on the ring sulfur atom, resulting in the formation of an acyclic internal phosphonium salt, which by subsequent elimination of a phosphine sulfide, closes to the four-membered ring.¹³⁰



¹²⁹ H. J. Federsel, J. Bergman, and U. Stenhede, *Heterocycles* **12**, 751 (1970).

¹³⁰ D. N. Harpp and J. G. Gleason, *J. Org. Chem.* **35**, 3258 (1970).

Thietanes can also be prepared by ring contraction of higher-membered heterocyclic rings. Thermolysis of the dithiolane dioxide **129** in benzene leads to *trans*-2-phenyl-3-benzoylthietane (**130**) and benzalacetophenone¹³¹ (Eq. 20).



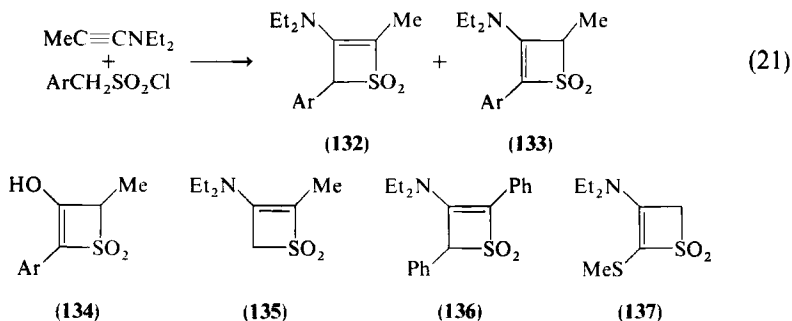
Solid **130** decomposes on further heating to **131** and polymeric thioformaldehyde.

Harpp *et al.*¹³² succeeded in preparing **130** by conversion of a cyclic disulfide with the substituted phosphines $\text{P}(\text{NMe}_2)_3$ and $(\text{NMe}_2)_3\text{P}=\text{S}$. Truce and Kao Liu⁵⁷ used nickel boride, inert to sulfones, for the same ring transformation.

B. THIETES

1. Cycloaddition

Cycloaddition of ynamines with sulfenes (generated from sulfonyl chlorides) to give thiete sulfones **132** and **133** has been reported by Truce *et al.*¹³³ (Eq. 21). Acid hydrolysis yields the corresponding enols (**134**). Other compounds that have been prepared in this manner are **135** and **136**.¹³⁴ Sulfene



¹³¹ A. Pawda and R. Gruber, *J. Org. Chem.* **35**, 1781 (1970).

¹³² D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Am. Chem. Soc.* **90**, 4181 (1968).

¹³³ W. E. Truce, R. H. Bavry, and P. S. Bailey, *Tetrahedron Lett.* **54**, 5651 (1968).

¹³⁴ A. Majid Hamid, *J. Chem. Soc. C* **13**, 1612 (1968).

also reacts with methylthio-1-(*N,N*-diethylamino) ethene in ether to give **137**.¹³⁵ The compounds **138–140** have been synthesized in a five-step reaction.¹³⁶

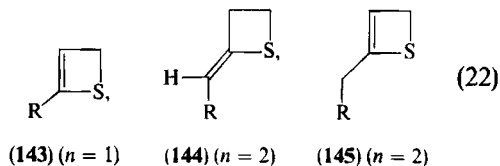
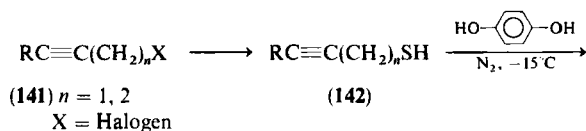


(138) $R = \text{COCH}_3$

(139) $R = \text{Ph}$

(140) $R =$

The thermally unstable acetylenic thiols **142**, which are produced from the corresponding halogen substituted acetylene derivatives **141**, have been reported to undergo, in the presence of hydroquinone and nitrogen at -15°C , heterocyclization to the derivatives **143**, **144**, and **145** (Eq. 22).¹³⁷



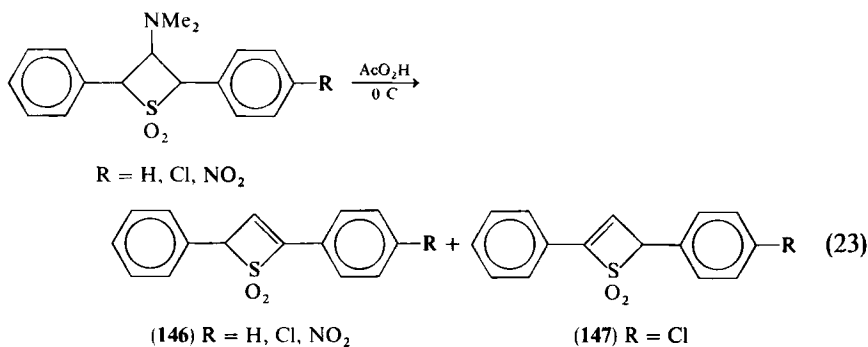
2. Elimination Reactions

Thietes can be prepared by elimination from appropriately substituted thietanes. 2,4-Diarylthiete 1,1-dioxides (**146** and **147**) were produced in good yields by peracid oxidation and intramolecular amine oxide elimination of 3-dimethylaminothietane 1,1-dioxides (Eq. 23).

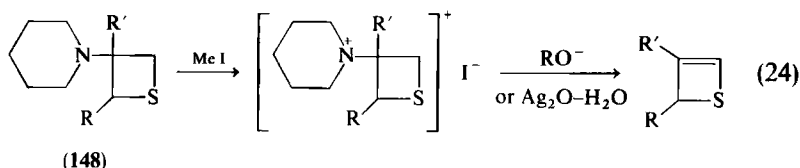
¹³⁵ N. P. Petukhove, N. E. Aristovo, A. U. Stepanyants, and E. N. Prilezhaeva, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1**, 132 (1976).

¹³⁶ B. H. Patwardhan, E. J. Parker, and D. C. Dittmer, *Phosphorus Sulfur* **7**, 5 (1979).

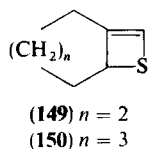
¹³⁷ J. Surzur, C. Dupuy, M. P. Crozet, and N. Aimar, *C. R. Acad. Sci, Ser. C*, **269**, 849 (1969).



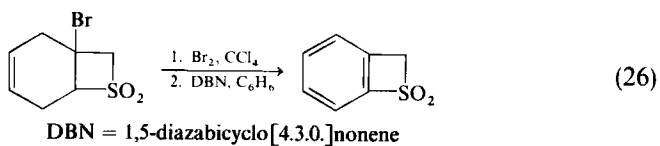
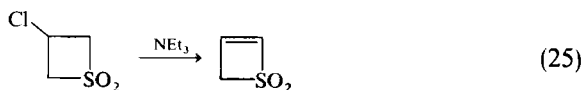
A general synthetic approach to the thietes is provided by a Hoffmann elimination from aminothietanes **148** (Eq. 24). Other thiete derivatives



prepared in this manner are the fused-ring structures **149** and **150**.⁶⁹



The oxides of thiete and benzothiete have been prepared from halogenated thietane oxides by elimination reactions.¹³⁸ (Eqs. 25 and 26)

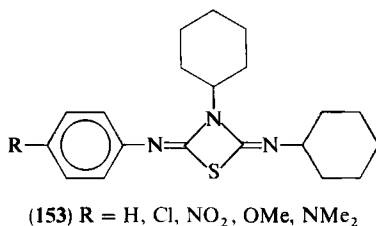
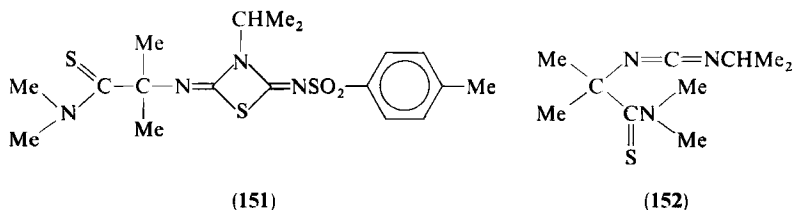


¹³⁸ D. C. Dittmer and T. R. Nelsen, *J. Org. Chem.* **41**, 3044 (1976).

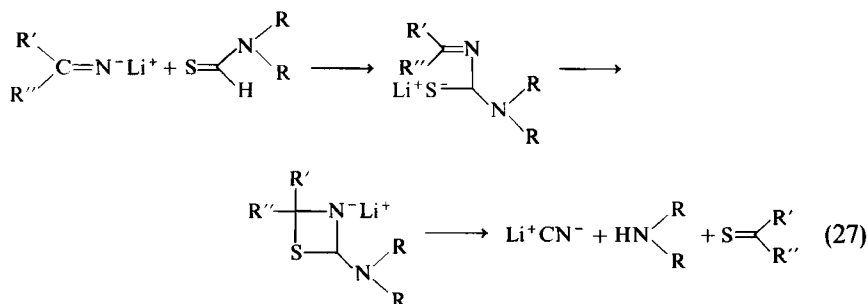
C. THIAZETIDINES

1. Cycloaddition

A successful method for preparing 1,3-thiazetidines is the cycloaddition of carbodiimides with isocyanates. The cycloadduct **151** was derived by the interaction of carbodiimide **152** and tosyl isothiocyanate⁵⁶. Reaction of **152** with methyl or phenyl isothiocyanate preferentially leads to iminotriazine-thiones. Cycloaddition between aryl isothiocyanates and dicyclohexylcarbodiimide produced **153**.¹³⁹



Thiazetidines have been observed as cyclic intermediates during a new kind of Wittig conversion (Eq. 27).¹⁴⁰

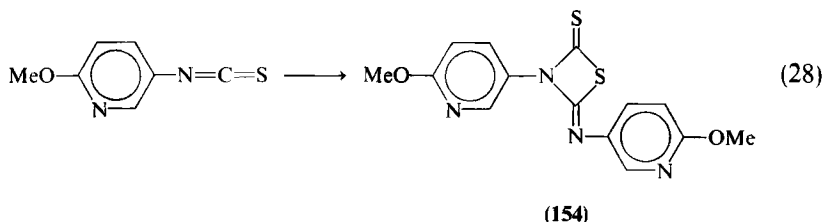


The cycloaddition of two isothiocyanate molecules, prepared by condensation of 6-methoxy-3-pyridinamine and thiophosgene, produces a new type

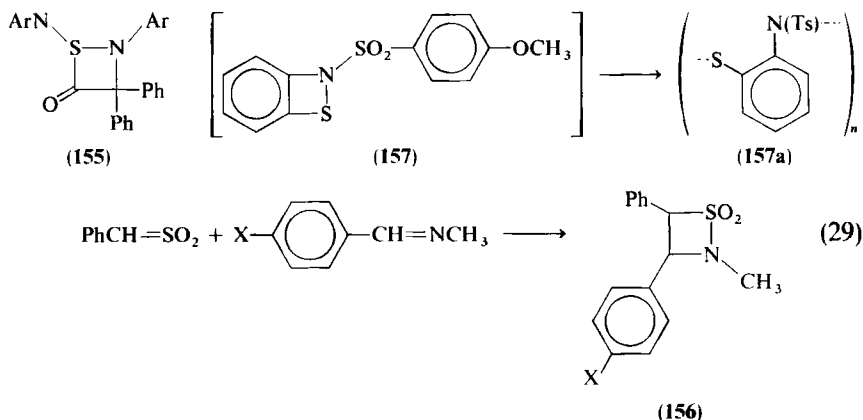
¹³⁹ O. Exner, V. Jehlick, and A. Dondoni, *Collect. Czech. Chem. Commun.* **41**, 562 (1976).

¹⁴⁰ R. Ahmed and W. Lwowski, *Tetrahedron Lett.* **41**, 3611 (1969).

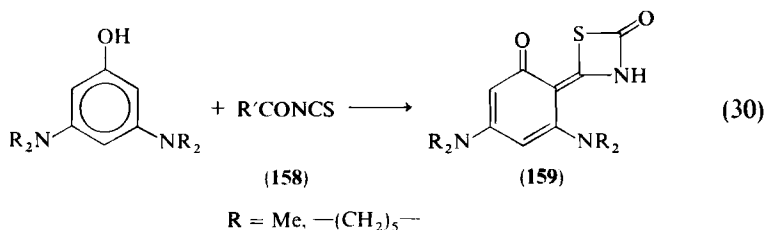
of dimer with 1,3-thiazetidine structure **154** (Eq. 28).⁶⁶ Heterocumulenes such



as sulfurdiiimide undergo cycloaddition with a ketone to 1,2-thiazetidin-2-ones (**155**).¹⁴¹ Sulfenes, produced *in situ* from sulfonyl chlorides with triethylamine, yield 1,2-thiazetidine 1,1-dioxides (**156**) with Schiff bases (Eq. 29).¹⁴²



Heimer and Field attempted to prepare a fused thiazetidine ring system by cycloaddition of *N*-sulfonylimidines with olefins or ketenes. Product **157** was found, however, to polymerize instantly to **157a**. By treatment of 3,5-diaminophenol with the isocyanate **158** the product **159** was obtained (Eq. 30).¹⁴³ Cycloaddition of benzoyl thiocyanates with *N,N'*-dicyclohexylcar-

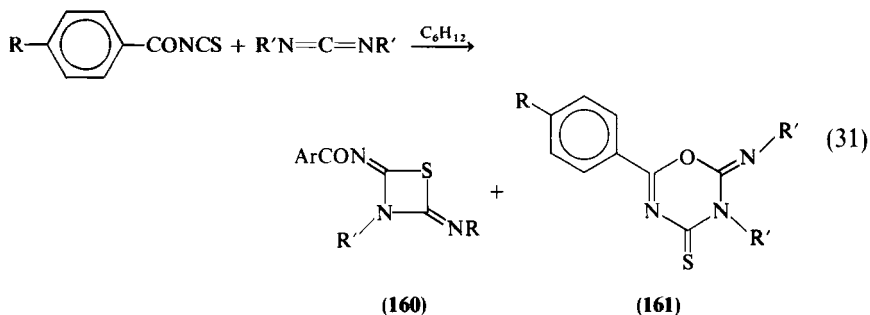


¹⁴¹ T. Minami, O. Aoki, H. Miki, Y. Oshiro, and T. Agawa, *Tetrahedron Lett.* **41**, 447 (1969).

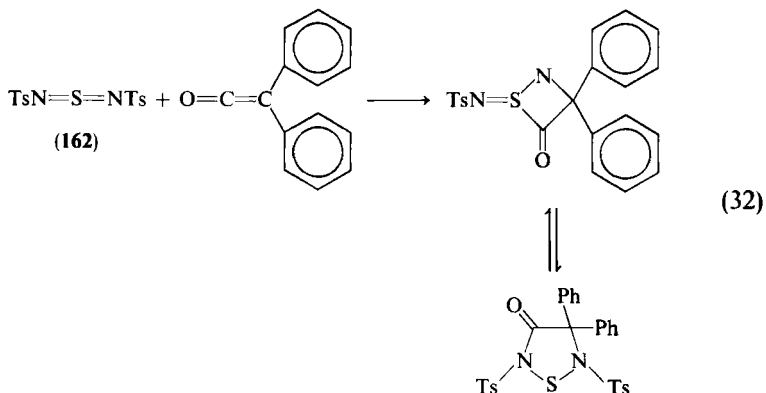
¹⁴² T. Hiraoka and T. Kobayashi, *Bull. Chem. Soc. Jpn.* **48**, 480 (1975).

¹⁴³ F. Effenberger and G. Kiefer, *Angew. Chem.* **79**, 936 (1967).

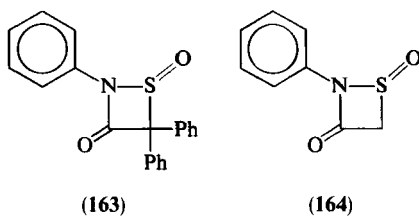
bodiimide or *N,N'*-diphenylcarbodiimide has been shown to yield a combination of four- and six-membered heterocycles **160** and **161**, respectively (Eq. 31).¹⁴⁴



A 2 + 2 cycloaddition of diphenylketenes with tosylated sulfur diimides **162** produces the 1,2-thiazetidin-3-one as well as the isomer 1,2-thiadiazolin-3-one (Eq. 32).¹⁴⁵ Reaction of a ketene with *N*-sulfinylaniline in acetone at



−78°C yielded *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (**163**).¹⁴⁶ Compound **164** was prepared earlier by a similar reaction.⁴⁶



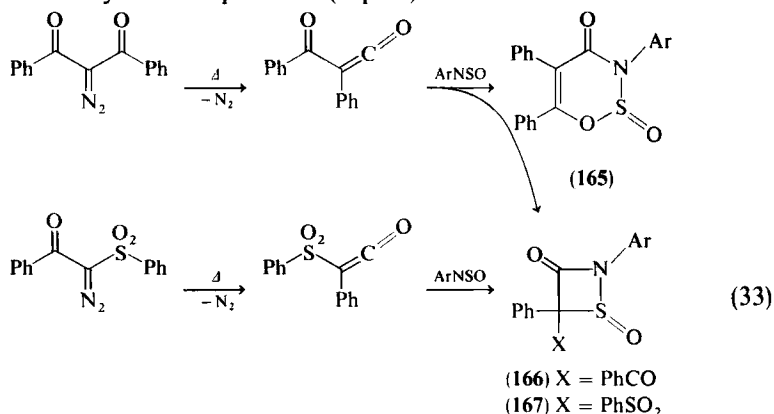
¹⁴⁴ O. Hritzova and P. Kristian, *Collect. Czech. Chem. Commun.* **43**, 3258 (1978).

¹⁴⁵ H. Grill and G. Kresze, *Tetrahedron Lett.* **17**, 1427 (1970).

¹⁴⁶ J. E. Semple and M. M. Jouillié, *J. Org. Chem.* **43**, 3066 (1978).

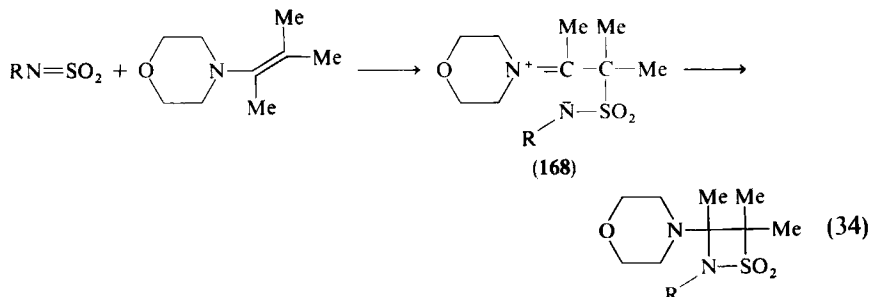
Often thiazetidines originate as by-products when six-membered heterocycles are produced.

A novel synthesis in which diazoketones are thermolyzed with *N*-sulfinylamines leads to cyclic *S*-oxides such as 3,4-dihydro-1,2,3-oxathiazine and 1,2-oxazetidine derivatives.¹⁴⁷ A similar synthesis utilizing diazodiketones yields, via a 4 + 2 cycloaddition, oxathiazines (**165**) and, via 2 + 2 cyclization, thiazetidines (**166**). When sulfonyldiazoketones were used, thiazetidines **167** were the only isolated products (Eq. 33).



A sulfonylimine that is formed *in situ* as a reactive intermediate by interaction of the corresponding aminosulfonyl chloride and triethylamine has proved to be a popular cycloaddition reagent in the synthesis of 1,1-thiazetidines.

In contrast to the sulfinylimines, the sulfonylimines are used only at a low temperature. Nagai *et al.*¹⁴⁸ have studied the reaction of a sulfonylimine with enamines that do not have any reactive hydrogen atoms in the molecule ("Type C" enamine). The cyclic product may be produced via a two-step mechanism in which a zwitterionic intermediate (**168**) occurs (Eq. 34). The



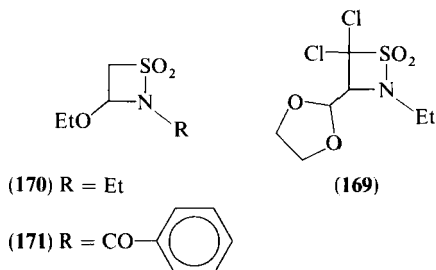
¹⁴⁷ L. Capuano, G. Urhahn, and A. Willmes, *Chem. Ber.* **112**, 1012 (1979).

¹⁴⁸ T. Nagai, T. Shingaki, M. Inagaki, and T. Ohshima, *Bull. Chem. Soc. Jpn.* **52**, 1102 (1979).

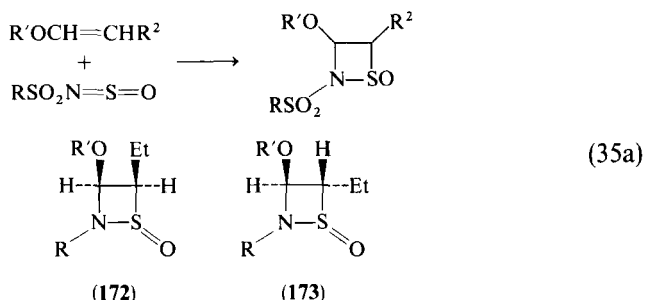
alternative mechanism for the formation of the cycloproduct would be a concerted $2 + 2$ cycloaddition.

An analogous reaction has been carried out with other alkenes such as 2-dichloromethylene-1,3-dioxalane to produce the thiazetidine **169**.¹⁴⁹

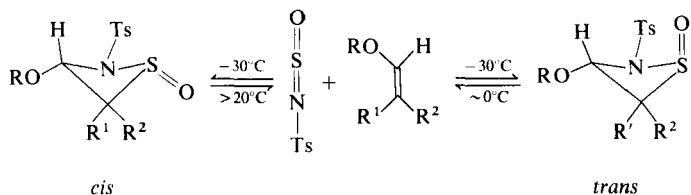
Ethylsulfonylimide and the more electrophilic *N*-sulfinylbenzimidate and a vinyl ether were used in the preparation of **170** and **171**.



N-Sulfinylsulfonimides treated with vinyl ethers give 1,2-thiazetidine 1-oxide (Eq. 35a).¹⁵⁰ Investigation of the stereochemistry of this reaction showed that no isomerization occurs between the forms **172** and **173**, which is the rule for the corresponding azetidines.¹⁴³



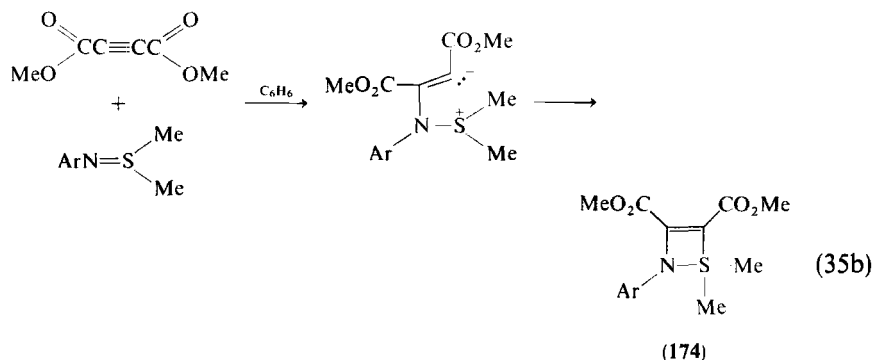
Most cycloadditions utilizing vinyl ethers to produce four-membered rings are stereospecific or at least stereoselective in relation to the vinyl ether.³⁷



¹⁴⁹ G. M. Atkins and E. M. Burgess, *J. Am. Chem. Soc.* **89**, 2502 (1967).

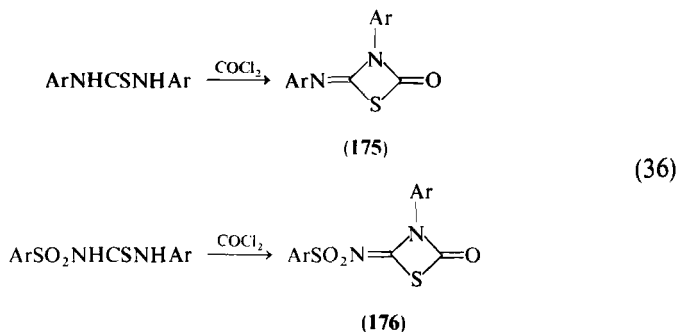
¹⁵⁰ F. Effenberger and R. Gleiter, *Chem. Ber.* **99**, 3903 (1966).

By treatment of iminosulfuranes with dimethyl acetylenedicarboxylate an unstable, 1,2-thiazetidine (**174**) was obtained.¹⁵¹ (Eq. 35b).



2. Eliminative Cyclization

Reaction of *N*-aryl thioureas with phosgene leads to the formation of the thiazetidine derivatives **175**¹⁵² and **176**¹⁵³ (Eq. 36). In contrast to **175**, the arylsulfonyl-substituted compound **176** is very unstable.



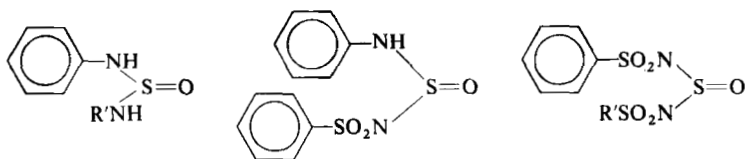
In a later study of these reactions, differently substituted thioureas were compared in relation to their effectiveness in producing four-membered rings.¹⁵⁴ Compounds **177** and **178** produced four-membered intermediates that collapsed to the more stable chlorformamidines. This phenomenon is most likely the result of the greater basicity of the *N*-alkyl than that of the *N*-aryl group.

¹⁵¹ Y. Hayashi, Y. Iwagani, A. Kadoi, T. Shono, and D. Swern, *Tetrahedron Lett.* **12**, 1071 (1974).

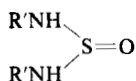
¹⁵² H. Ulrich and A. A. R. Sayigh, *Angew. Chem.* **78**, 761 (1966).

¹⁵³ W. Will, *Ber. Dtsch. Chem. Ges.* **14**, 1486 (1881).

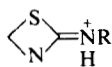
¹⁵⁴ H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Tetrahedron* **22**, 1565 (1966).



(177) R = H, Me
R' = alkyl



(178)

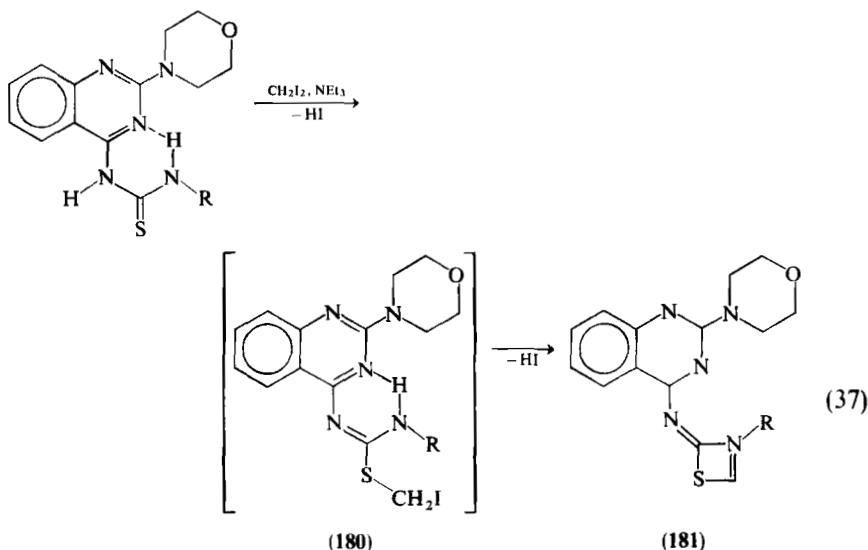


(179)



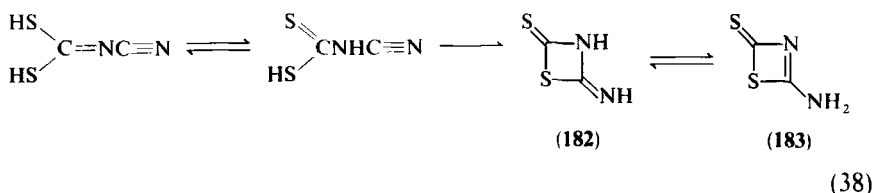
Another type of cyclization reaction with thioureas has been observed by Ueno *et al.*⁵³ Here 1,3-thiazetidin-3-ylum salts (179) are obtained in good yields by treatment of chloromethylsulfoxide with substituted thioureas followed by treatment of the resulting isothiuronium chlorides with concd H_2SO_4 and NaBPh_4 . The methanesulfinyl unit acts as the leaving group in this cyclic nucleophilic substitution reaction.

Thioureas carrying one substituent capable of intramolecular hydrogen bonding produce good yields of the possible isomers of 2-amino-1,3-thiazetidines (181) when treated with methylene iodide in the presence of triethylamine.⁵¹ A two-step reaction mechanism is assumed, although the existence of the intermediate 180 could not be substantiated (Eq. 37). The cyclization reaction can be improved by increasing the nucleophilic character of the nitrogen atom with an electron-donating substituent R.



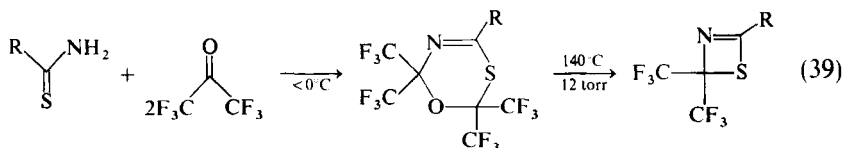
The same reaction carried out with unsymmetrically disubstituted thio-ureas not able to participate in intramolecular hydrogen bonding produced thiazetidine derivatives in poor yields.⁵²

Intramolecular cyclization of *N*-cyanodithiocarbamic acid leads to the formation of 2-thio-4-amino-1,3-thiazete (**183**) and its tautomer 2-thio-4-imino-1,3-thiazetidene (**182**) (Eq. 38).⁷⁷ The four-membered heterocycle is a finely crystalline, red-colored compound that decomposes at 172°C.

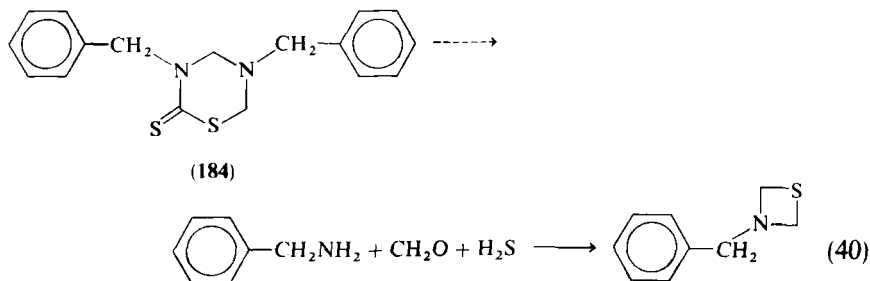


3. Ring Contraction of Other Heterocycles

Burger *et al.* first introduced 2*H*-1,3-thiazete as a new heterocyclic system.¹⁵⁵ By utilizing the stabilizing effect of trifluormethyl groups on strained-ring systems, they succeeded in reducing the size of a substituted oxathiazine ring to the thiazete system. The reaction proceeds via a thermally induced retro Diels–Alder mechanism with subsequent electrocyclization (Eq. 39).



Solvolysis of the thiadiazine **184** leads to gradual elimination of a variety of small aliphatic molecules. They have been observed to recombine partly to four-membered N,N- and N,S-containing heterocycles via secondary condensation reactions¹⁵⁶ (Eq. 40). It is proposed that the antimicrobial action of thiadiazines can in part be correlated to their hydrolysis products.



¹⁵⁵ K. Burger, J. Albanbauer, and M. Eggersdorfer, *Angew. Chem.* **87**, 816 (1975).

¹⁵⁶ G. Würbach, D. Martin, and A. Rieche, *Pharmazie* **26**, 78 (1971).

VI. Chemical Properties and Reactions

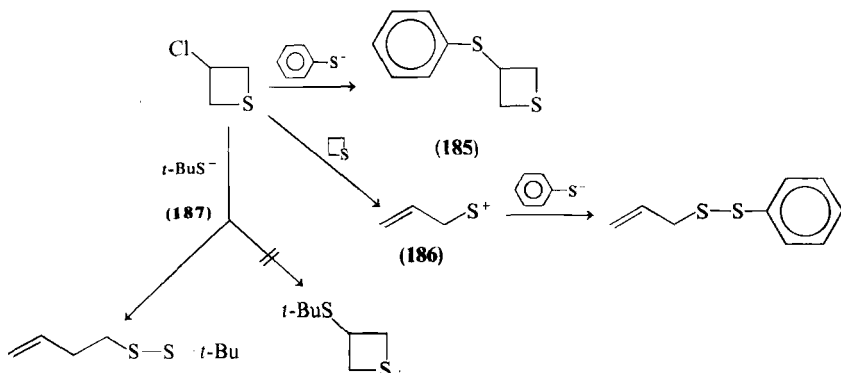
A. THIETANES

1. Reactivity and Derivatization

As has been pointed out in the review by Sander, the thietane ring can be positioned between the highly reactive thiiranes and the more indifferent thiophenes.¹ During the course of the reaction the three-membered ring structure rarely remains intact, whereas the five-membered ring is mostly stable. Depending on the reaction conditions, the thietane ring can behave in both ways. Addition reactions at the free-electron pair of the sulfur atom mostly leave the ring intact.

The lower amount of ring strain renders thietane molecules more resistant to thermolytic and photolytic degradation. Nonetheless, to prevent decomposition, they still must be stored in the dark and at room temperature.

Reactions of halogenated thietane derivatives have been studied by Nuretdinova *et al.*¹⁵⁷ Differences in reactions of 2-chlorothietane with potassium phenoxide and with thiophenoxide had been observed, which were correlated to the Pearson principle of strong and weak bases, the phenoxide ion corresponding to a "weak" base. The reaction of thiophenoxide with the thietane can either lead to the substitution product **185** or by rearrangement of the intermediate thietane cation to the acyclic ion **186**. Experiments have also been carried out with a stronger base such as the alkylsulfide ion **187** (Scheme 7). In general, the yield of thietane derivatives is directly proportional to the acid-base strength.

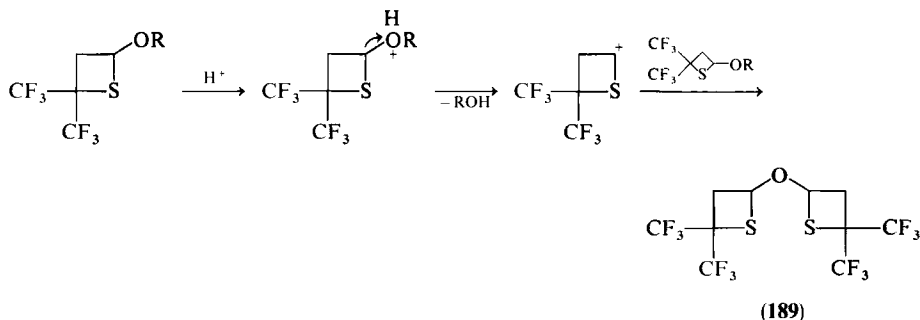
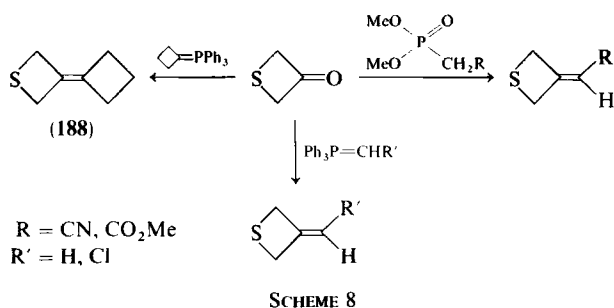


SCHEME 7

¹⁵⁷ O. N. Nuretdinova and B. A. Arbuzov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **3**, 3550 (1972).

3-Chlorothietane was subjected to reaction with dichloro derivatives of phosphorous acid to give, after heating the reaction mixture to 150°C, the acyclic compound thiophosphoric acid in low yields.¹⁵⁸

For the purpose of studying the degree of 1,3-transannular interaction of four-membered rings because of the relatively small 1,3-carbon-carbon or -carbon-heteroatom distances, new members of the thietane group were synthesized. Treatment of thietan-3-one with various phosphorus ylides in ether led via the Wittig reaction and its variations to the following array of compounds (Scheme 8), of which 3-cyclobutylidenethietane (**188**) is the only liquid at room temperature. Dithietane ethers (**189**) were prepared in good yields by protonation of 4-alkoxy-2,2-bis(trifluoromethyl)thietanes and subsequent elimination of alcohol and electrophilic substitution of the resulting carbocation (Scheme 9).¹⁵⁹



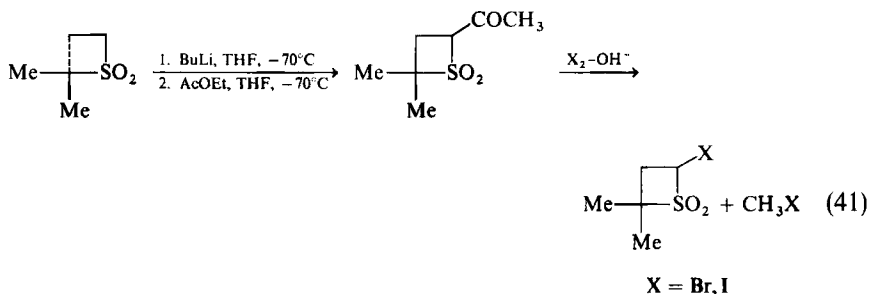
SCHEME 9

Halo- or 2-acylthietane 1,1-dioxides could not be prepared by direct halogenation or acylation of the heterocycle. Better results were attained by

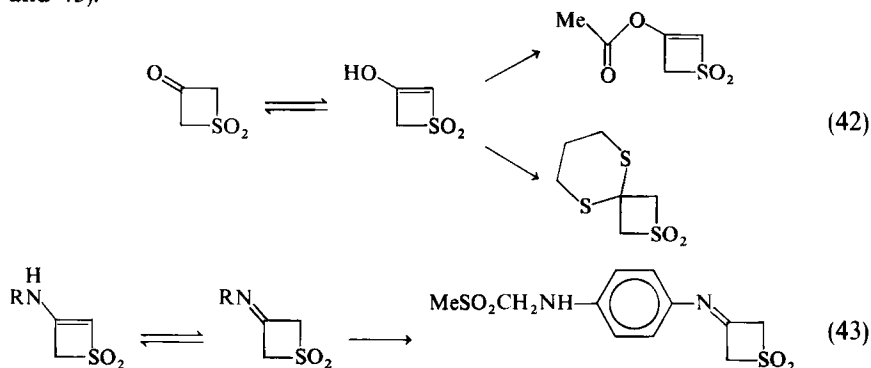
¹⁵⁸ O. N. Nuretdinova and B. A. Abuzov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **10**, 2225 (1971).

¹⁵⁹ G. Seitz and H. Hoffmann, *Chem.-Ztg.* **100**, 440 (1976).

initial activation of the thietane with butyllithium at -70°C prior to treatment with ethyl acetate and subsequent halo substitution⁷⁰ (Eq. 41).



By specific derivatization of thietanone and thietanimine dioxides, the tautomeric preference for the keto or enol form could be ascertained (Eqs. 42 and 43).⁸⁰

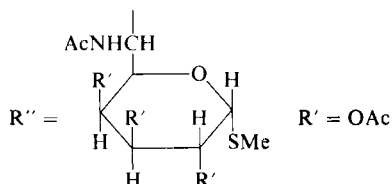
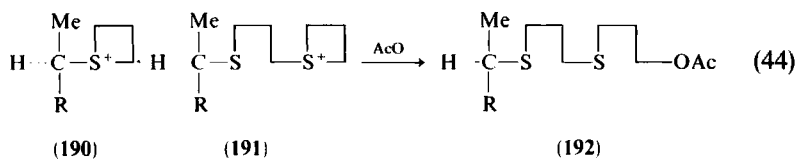


2. Formation and Behavior of Thietanonium Ions

Thietanonium ions have been observed quite frequently either as intermediates or as isolated stable salts. Treatment of an activated carbohydrate epimer, a constituent of the antibiotic lincomycin, with thietane led to the sulfonium salt **190**. By nucleophilic attack with acetate ions the ring could be opened and the process mentioned above repeated so that compound **191** results.¹⁶⁰

Further acylation leads to the open-chain aliphatic product **192**, which could then be transformed to the next higher thietane homolog. (Eq. 44). By protonation of thietane with $\text{FSO}_3\text{I--SbF}_5\text{--SO}_2$ at -60°C , a thietanonium ion emerged that could be detected by NMR spectroscopy.⁶¹ A sul-

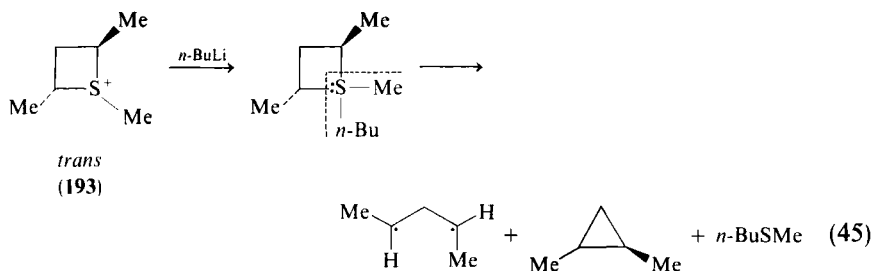
¹⁶⁰ B. Bannister, *J. S. Perkin I*, 274 (1974).



fonium ylide has been observed as an intermediate during the thermal reaction of thietane with dimethyl diazomalonate in the presence of CuSO_4 in the rearrangement to the corresponding thiophene.¹⁶¹

Unusual fragmentation reactions for thietanium salts have been observed.¹⁶² Their analysis may reveal more information about the influence of *d*-orbitals in the reaction mechanisms of organosulfur compounds. Alkylation of certain thietanes leads to 5-methylthietaniumium salts. The thietanium salt **193**, which is formed from 2,4-dimethylthietane and $(\text{CH}_3)_3\text{O}^+\text{BF}_4^-$, breaks up when treated with *n*-butyllithium into a reactive biradical and its resulting cyclopropane and a thioether.

The reaction is initiated by the attack of the organolithium at sulfur to produce the pentacoordinate sulfur species. This seems to be the prime reaction of all electron-deficient sulfur compounds with organolithiums (Eq. 45).



3. Ring Expansion

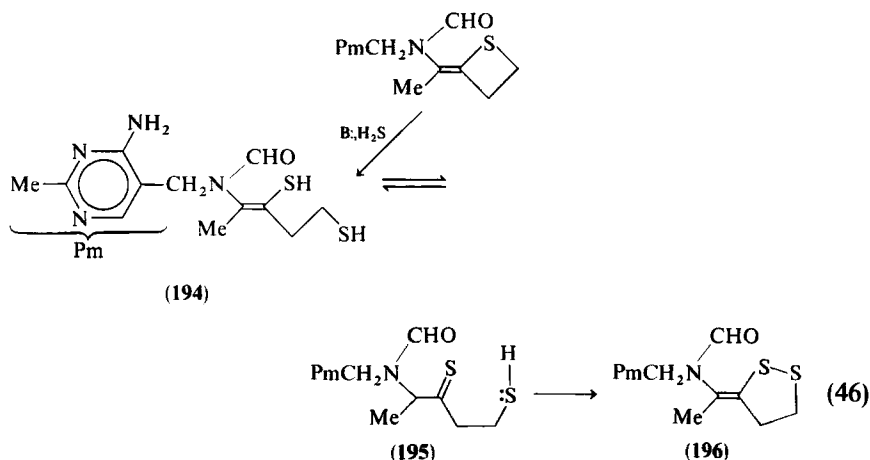
Thiethanes are often utilized as starting materials for a variety of different chemical systems.

¹⁶¹ W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.* **37**, 1721 (1972).

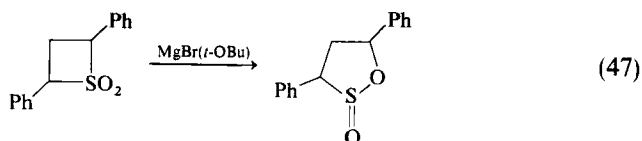
¹⁶² B. M. Trost, R. W. La Rochelle, and R. C. Atkins, *J. Am. Chem. Soc.* **91**, 4320 (1969).

High temperatures (250°C, Al_2O_3) cause ring enlargement to thiophenes.¹

Treatment of thietanes with hydrogen sulfide in dimethylformamide leads to a ring expansion reaction in which 1,2-dithiolanes (**196**) are formed.¹⁶³ The reactions were carried out with thiamine anhydride. By base-induced proton elimination the thietane ring is opened; recombination of the resulting acyclic anion with the proton and addition of H_2S to the double bond results in the formation of an enethiole (**194**)³⁰ (Eq. 46). Intramolecular cyclization of the tautomeric thioketone **195** leads thus to the five-membered heterocycle (Eq. 46).



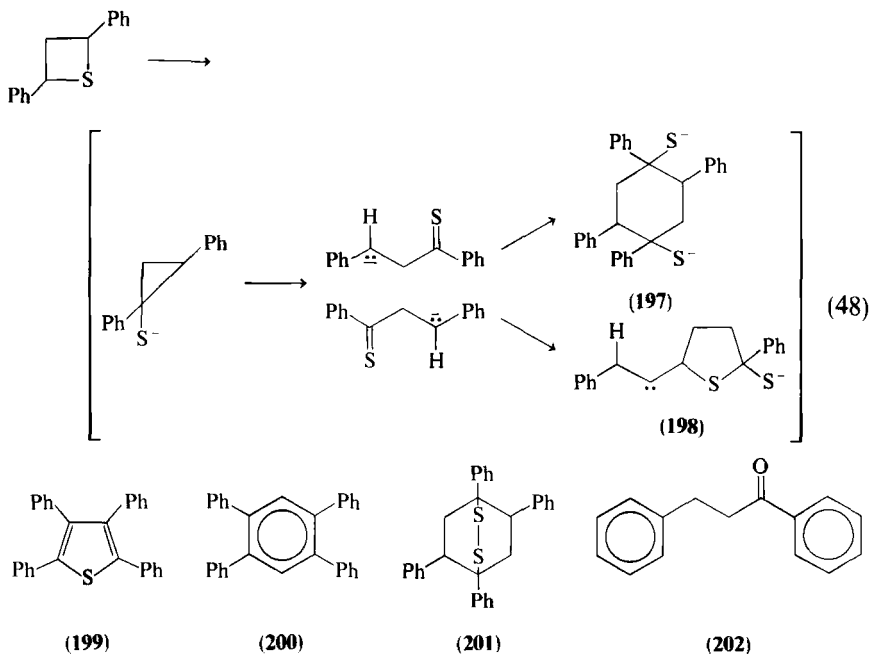
Special reagents such as *tert*-butoxymagnesium bromide can cause rearrangement of the thietane 1,1-dioxides to the cyclic sulfinate structure¹⁶⁴ (Eq. 47). This ionic base-catalyzed stereospecific rearrangement takes place at moderate temperatures; its mechanism is proposed to resemble that of the Stevens rearrangement. Nuclear magnetic resonance studies showed that the *cis* sulfone is rearranged to the *cis* product; the *trans* sulfone initially rearranged to the *trans* product but eventually changed to the *cis* configuration.



By treatment of 2,4-diphenylthietane with potassium *tert*-butoxide in dimethylformamide, a dark brown viscous oil is obtained, in which different products could be detected. Some of these were identified as cyclic products

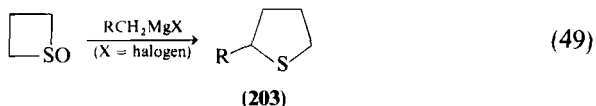
¹⁶³ A. Takamizawa, K. Hirai, and T. Ishiba, *Tetrahedron Lett.* **6**, 441 (1970).

that resulted from a modified version of a Stevens rearrangement (Eq. 48).¹⁶⁴ In addition to **197** and **198**, the structures **199**, **200**, **201**, and **202** were identified.



Similar ring expansion reactions 1,2-dithiolanes were observed when thiethanes, after base $[(\text{Et})_2\text{NH}-\text{DMFA}]$ -catalyzed ring opening, were heated with sulfur.^{70,165}

The formation of α -substituted thiolanes **203** in 40–70% yields was observed by reactions of trimethylene sulfoxide with organomagnesium compounds (Eq. 49).¹⁶⁶



Much research into the ring-enlargement reactions of thietanes has been done by Takamizawa *et al.*^{167–169} A variety of reactions were carried out

¹⁶⁴ R. M. Dodson and J. Yu Fan, *J. Org. Chem.* **36**, 2708 (1971).

¹⁶⁵ S. Yurughi, H. Yonemoto, T. Fushini, and M. Numata, *Yakugaku Zasshi* **80**, 1691 (1961).

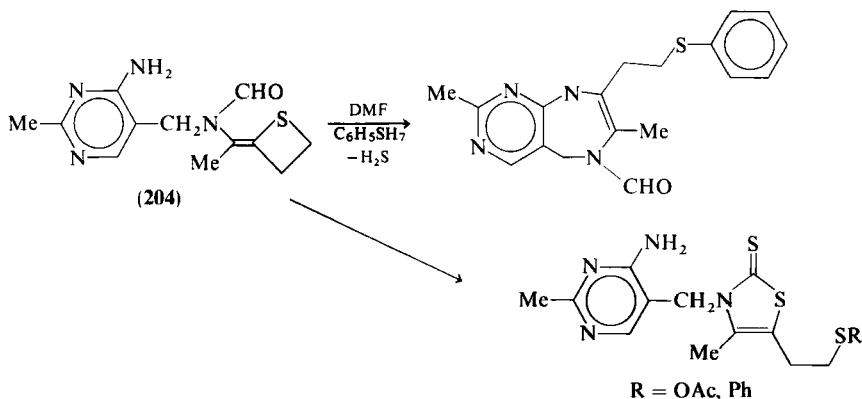
¹⁶⁶ N. A. Nesmeyanov and V. A. Kalyavin, *CA* **86**, 29554 (1974).

¹⁶⁷ A. Takamizawa, K. Hirai, and I. Ishiba, *Chem. Pharm. Bull.* **19**, 1022 (1971).

¹⁶⁸ A. Takamizawa, K. Hirai, and I. Ishiba, *Chem. Pharm. Bull.* **19**, 2009 (1971).

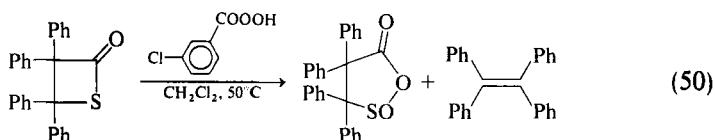
¹⁶⁹ A. Takamizawa, K. Hirai, and I. Ishiba, *Chem. Pharm. Bull.* **19**, 2222 (1971).

with thiamine anhydride (**204**) and various reagents, which led to different heterocyclic derivatives (Scheme 10).

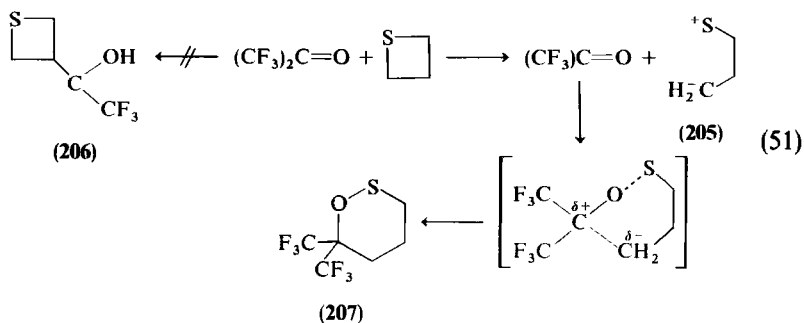


SCHEME 10

Kohn *et al.*¹⁷⁰ developed a one-step preparation of a stable carboxylic-sulfinic acid anhydride by oxidizing 3,3,4,4-tetraphenyl- β -propionothiolactone with a peracid (Eq. 50).



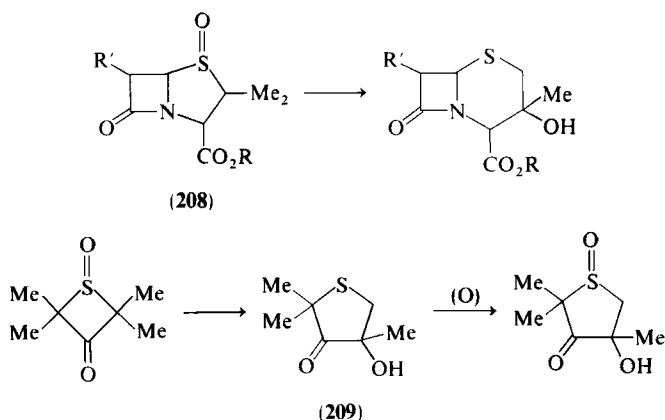
When hexafluoroacetone is treated with thietane (2:1) a concerted addition results in the formation of a six-membered ring (Eq. 51).¹⁷¹ Here the excited state **205** seems to favor the formation of the six-membered ring structure **207** over the corresponding thietane derivative **206**.



¹⁷⁰ H. Kohn, P. Charumilind, and S. H. Simons, *J. Am. Chem. Soc.* **101**, 5432 (1979).

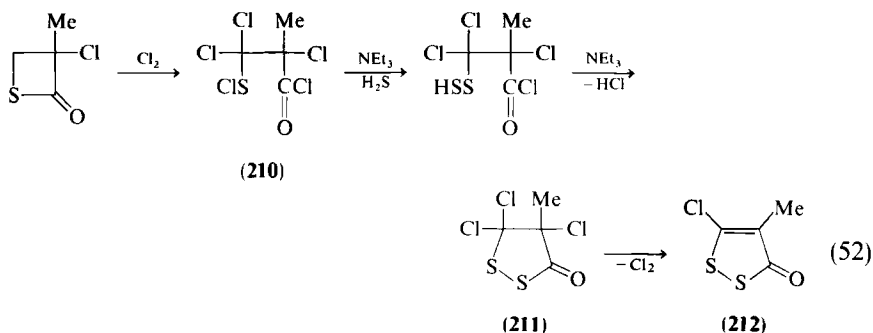
¹⁷¹ O. Mir and J. M. Shreeve, *Inorg. Chem.* **19**, 1510 (1980).

An interesting reaction related to the ring expansions of penicillin *S*-oxides (208) was observed in the thermal rearrangement of 2,2,4,4-tetramethylthiethan-3-one 1-oxide to the five-membered thiolane ring 209.¹⁷² Oxidation attempts of these thermally unstable thietanone oxides led via ring opening to the more stable heterocycle. The reaction mechanism (Scheme 11) was



SCHEME 11

studied by trapping the intermediates with silylating agents. The chlorination of 3,3-methylchloro-2-thietanone at -20°C leads to the acyclic structure 210 from which the five-membered heterocycle 211 can be formed after treatment with hydrogen sulfide and cyclocondensation of the resulting thiole by elimination of HCl .¹⁷³ Expulsion of Cl_2 leads to (212) (Eq. 52).



Oxidation of tetraphenylthietan-2-one with a peracid produces, via two possible pathways, 3,3,4,4-tetraphenyl-1,2-oxathiolan-5-one 2-oxide.¹⁷⁰ Ring

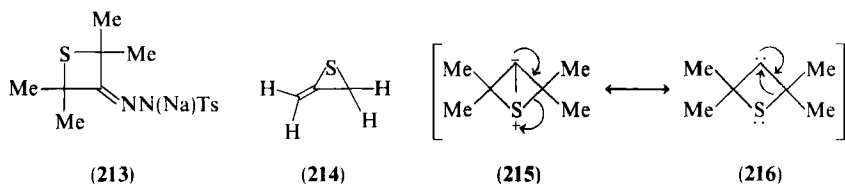
¹⁷² R. L. Bushby, *J. S. Perkin I*, 2590 (1976).

¹⁷³ T. P. Vasil'eva, M. G. Lin'kova, O. V. Kil'disheva, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.* 9, 2108 (1980).

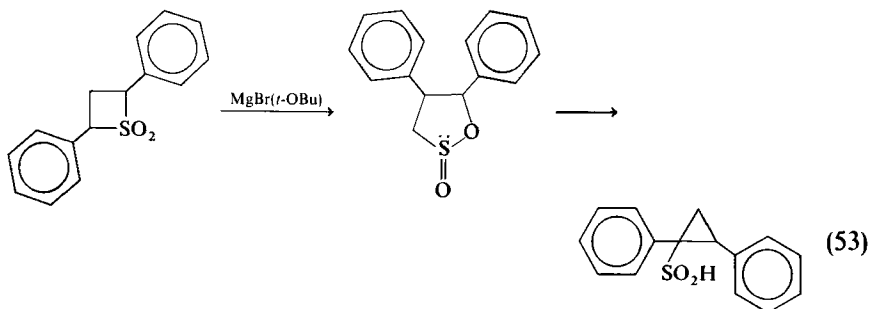
enlargement to pyrazol derivatives has been observed by treatment of thietane-2-thione with hydrazine.⁶⁶

4. Ring Contraction

Heating of thietanes can often lead to a ring contraction. Thermal treatment (150°C, *in vacuo*) of the tosylhydrazide salt **213** gives the allene episulfide **214**, a unique synthesis for this molecule.¹⁷⁴ The mechanism is suggested to proceed either via the intermediate bicyclobutane ylide **215** or the mesomeric structure **216**. Dodson *et al.* have noticed the rearrangement



of 2,4-diphenylthietane 1-oxide and 1,1-dioxide to cyclopropane derivatives¹⁷⁵ (Eq. 53).



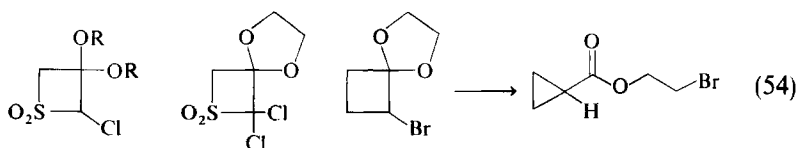
The same has been observed by Dodson and Klose in previous work where *cis*- and *trans*-1,2-diphenylcyclopropane were formed by pyrolysis of 2,3-diphenylthietane 1,1-dioxide at 230°C. Analogous results have been achieved by both photolysis and thermolysis of 1-phenyl-2-benzoylthiethane 1,1-dioxide to a *cis*-*trans* mixture of 1-phenyl-2-benzoylcyclopropane.¹⁷⁶

Paquette has used the chloroketal derivatives of thietane 1,1-dioxide as an especially well-suited model for the theoretical study of the thermally induced intramolecular six-electron ring contraction rearrangement, which is pointed out in Eq. (54) for the ketals of 2-bromocyclobutanone that give cyclopropylcarboxylates.⁷⁹ Desulfurization of thietanes to cyclopropane did not prove too successful.¹⁰²

¹⁷⁴ A. G. Hartmann and A. Bhattacharjya, *J. Am. Chem. Soc.* **98**, 7081 (1976).

¹⁷⁵ R. M. Dodson, P. D. Hammen, and J. Y. Fan, *J. Org. Chem.* **36**, 2703 (1971).

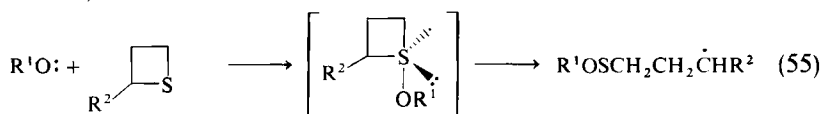
¹⁷⁶ R. M. Dodson and G. Klose, *Chem. Ind. (London)*, 450 (1963).



Flash vacuum pyrolysis (FVP) represents a special method for inducing decomposition of thietane compounds. Block *et al.* succeeded for the first time in the preparation of methylene sulfine in the gas phase, applying this method to thietane 1-oxide.^{6,177} The reaction starting at 600°C was followed by mass and microwave spectroscopy.

5. Ring Opening

While examining the interaction of thietanes with photochemically generated oxygen-centered radicals, it was found that ring opening is brought about by an initial attack on the sulfur atom (Eq. 55).^{177a} The reactions were carried out in cyclopropane and were directly followed by means of ESR spectroscopy. At temperatures below 230 K the sulfur-centered radical could be detected by ESR as an intensive signal showing a 1:2:1 triplet splitting ($g = 2.0098$).

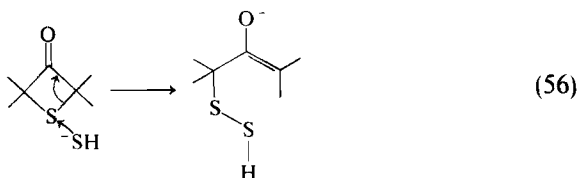


$\text{R}^1 = t\text{-Bu, Et, or Me}_3\text{Si}$

$\text{R}^2 = \text{H, Me}$

Homolytic ring opening of thietanes also resulted from reaction with pentafluorophenyl radicals, which were generated by photolysis of $\text{C}_6\text{F}_5\text{I}$ in the presence of $\text{Me}_3\text{SnSnMe}_3$.

A ring opening of the thietanone molecule can easily be induced by thio-ophile attack of hydrogen sulfide ions, which leads to the formation of an enolate ion (Eq. 56). This reaction also depends on the degree of methylation



¹⁷⁷ E. Block, R. E. Penn, M. D. Ennis, T. A. Owens, and S. L. Yu, *J. Am. Chem. Soc.* **100**, 7436 (1978).

^{177a} J. S. Chapman, J. W. Cooper, and B. P. Roberts, *J. C. S. Chem. Commun.*, 407 (1976).

at C-2 and C-4. The rate of ring opening is reduced by higher-methylated compounds because of steric hindrance by the methyl groups.

As pointed out in Section VI,A,1, the chlorination of 2-thietanones can lead to the break up of the C—S bond.¹⁷⁰

Alkylolithium cleaves the ring of cyclic sulfides. Attack of the carbanion on the sulfur atom opens the rings and forms a new carbanion.¹⁷⁸

6. Photochemistry

Photochemical decomposition of cyclic compounds proceeds by two different primary photolytic processes. The molecule may decompose either by direct fragmentation or by intramolecular rearrangement. Thietanes have not been investigated in as much detail as the thiophenes.

The photochemistry of thietanes involves entirely different pathways from those encountered in azetidines; the low bond dissociation energy of the C—S bond seems to be mainly responsible. The direct photolysis of thietane vapor with 213.9–228.8- and 253.7-nm light leads to ethylene and propylene, cyclopropane, and thiocyclopropene. A white polymer appeared as a constant by-product.^{178,179}

Photolysis of *trans*-2-phenyl-3-benzoylthietane yields both *cis*- and *trans*-1,3-diphenyl-2-ethenyl ketone and polymeric thioformaldehyde instead of the anticipated thiophene derivative.

Dice and Steer^{180,181} studied the photodecomposition of thiethanes for the main purpose of acquiring more insight into the chemistry of the fragmentation product thioformaldehyde. Photolysis of thietane vapor, irradiated with a 500-watt high-pressure mercury lamp (313 nm) through a $\text{NiSO}_4\text{--K}_2\text{CrO}_4$ filter, resulted in the formation of thioformaldehyde, ethylene, propylene, and 1,2-dithiocane (DTO). When cyclopentadiene is used with thietane, a fused ring, the 2-thiabicyclo[2.2.1]hept5-ene (TBH) (217) is produced. Its yield is directly proportional to the cyclopentadiene concentration. The reaction scheme is thought to involve a series of 1,4-biradicals (Scheme 12).

Although the photochemistry of the thietane ring has been studied to some degree in the gas phase,^{178,182} the study of its decomposition in solution or in glassy matrices has not been extensive. Biradicals are postulated as intermediates in order to account for the differences in stereochemistry, abiding by the Woodward–Hoffmann rules for concerted reactions. Biradi-

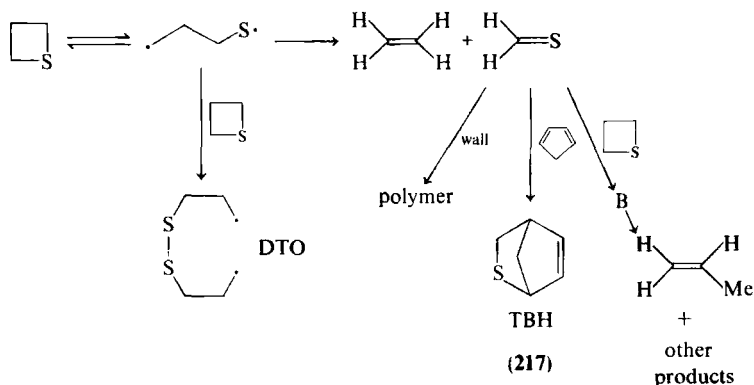
¹⁷⁸ H. A. Wiebe and J. Heckla, *J. Am. Chem. Soc.* **92**, (1970).

¹⁷⁹ A. Pawda, *Acc. Chem. Res.* **4**, 48 (1971).

¹⁸⁰ D. R. Dice and R. P. Steer, *Can. J. Chem.* **52**, 3518 (1974).

¹⁸¹ D. R. Dice and R. P. Steer, *Can. J. Chem.* **53**, 1744 (1975).

¹⁸² A. Pawda and R. Gruber, *J. Org. Chem.* **35**, 1781 (1970).

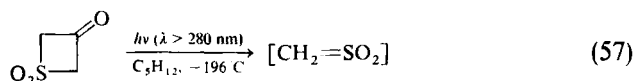


cals are important intermediates in photochemical and thermal decompositions. Dice *et al.* investigated the formation of hot 1,4-biradicals from direct photolysis (313 nm) of 3-ethyl-2-propylthietane.¹⁸¹

Padwa and Gruber¹⁸² already stressed the unusual rearrangements that occur upon irradiation of thietanes. The ground-state chemistry of substituted thietanes received considerable attention prior to 1970 but not the phototransformation of the ring system. Whereas azetidine analogs rearrange to pyrroles, thietane 1,1-dioxides contract under SO_2 evolution (because of the low bond dissociation energy of the C—S bond) to the cyclopropane ring system.

Four-membered rings and their heterocyclic analogs that contain one or two carbonyl functions can follow three principal reaction paths when photolyzed in solution. Depending on the nature of the substituents, the mode of reaction can be (1) decarbonylation, (2) cycloreversion, or (3) ring expansion.

In order to clarify the photolytic behavior of thietanones, Langendries *et al.*⁴⁸ monitored their reactions directly by IR spectroscopy in a cryostat.⁶ With the appearance of their specific IR absorption bands the sulfenes could be instantaneously detected and a cycloreversion mechanism postulated (Eq. 57). The sulfene bands could not be observed, however, when light with wavelengths below 220 nm was used for the irradiation.



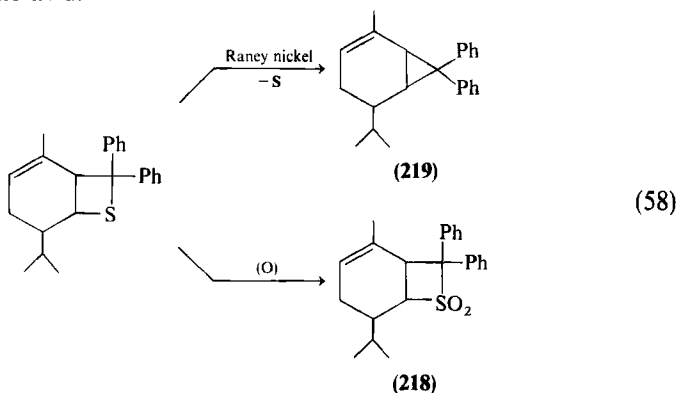
7. Thermolysis and Pyrolysis

At temperatures over 20°C , thietanes are likely to undergo ring enlargement or ring opening. Pyrolysis of the sulfones at temperatures above 900°C

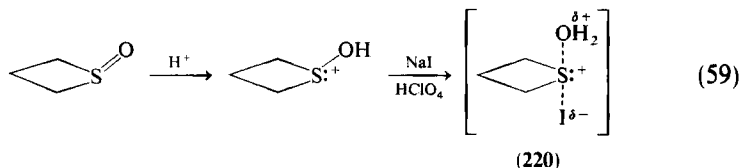
entails decomposition to cyclopropane and propene under SO_2 expulsion and to sulfenes and olefins as 2 + 2 cycloreversion products.¹⁰²

8. Oxidation and Reduction

Whereas oxidation leaves the fused thietane derivative **218** intact by giving the corresponding sulfone, reduction produces the 4-isopropyl-1,1-diphenylbicyclo[4.1.0]hept-1-ene (**219**) by extrusion of sulfur¹⁰⁶ (Eq. 58). The general oxidation procedure to convert thietanes to their sulfones comprises refluxing with peracetic acid.



Theoretical aspects of the effect of ring size on the acid-catalyzed reduction of cyclic sulfoxides by iodide ions have been studied by Tamagaki *et al.*,¹⁸³ who noticed that differences in reactivity are mainly dependent on the change in activation entropy, which is correlated to the rigidity of the transition complex **220**, (Eq. 59).



9. Solvolysis

Although 3,3-diethoxythietane 1,1-dioxide yields the corresponding thietan-3-one upon hydrolysis, the same treatment applied to its α -halogenated derivatives resulted in ring opening.⁸⁰

¹⁸³ S. Tamagaki, M. Mizuno, H. Joshida, H. Hiroto, and S. Oae, *Bull. Chem. Soc. Jpn.* **44**, 2456 (1971).

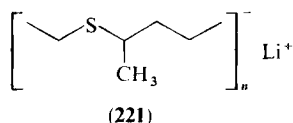
10. Polymerization

Thietanes all have, to varying degrees, the tendency to polymerize. The rate of polymerization is mainly dependent on the conditions. In sunlight the process takes place at a relatively slow rate. The strained polycyclic thietanes, such as 6-thiobicyclo[3.3.1]heptane polymerize spontaneously when photon or proton initiated.¹

The photocatalyzed polymerization of thietanes makes it very difficult to utilize them in other photochemical reactions, and often special handling and reaction procedures are required.

In one case, polymerization could be prevented by gradual extraction of the thietane from an inert solvent, such as *n*-pentane or petroleum ether, into the reaction medium.⁶¹

The ring-opening effect of alkyllithium on cyclic sulfides (Section VI,A,5) can be utilized for the formation of linear polymers of the general formula **221** when an excess of thietane is used.¹⁸⁴



11. Stereochemistry and Kinetics

The steric effects and rate constants for the reaction of cyclic sulfides, such as thietane with chloramine I ($\text{H}_3\text{CC}_6\text{H}_4\text{NCl}^-\text{Na}^+$), in which the sulfides are converted to sulfimides and sulfoxides, have been investigated.¹⁸⁵

B. THIETES

1. Reactivity and Thermal Stability

Thietes have been intensively investigated by Dittmer *et al.*,^{186–188} who have also written a review on the subject. The chemical behavior of thiete and its derivatives is very diverse. They exhibit a relatively high ring strain that offers a variety of synthetic applications.⁶⁹

¹⁸⁴ M. Morton and R. F. Kammereck, *J. Am. Chem. Soc.* **92**, 3216 (1970).

¹⁸⁵ F. Ruff, K. Komoto, N. Furukawa, and S. Oae, *Tetrahedron* **32**, 2736 (1976).

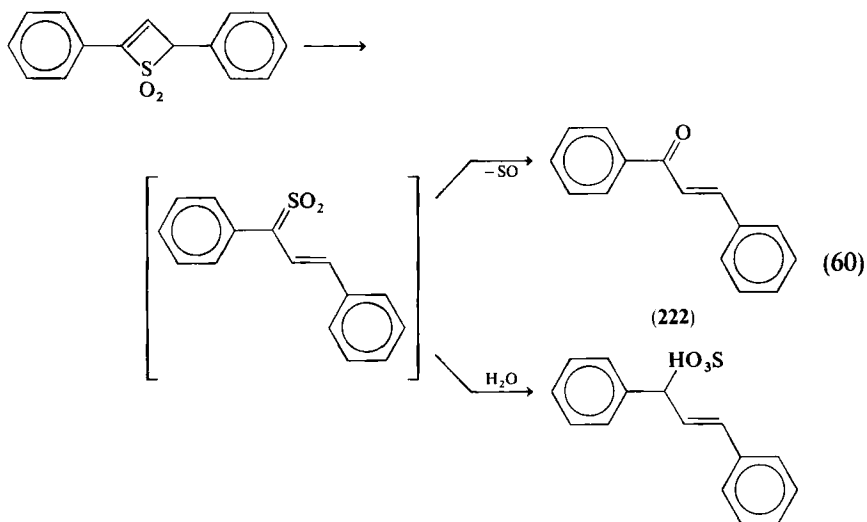
¹⁸⁶ D. C. Dittmer, P. L. F. Chang, F. A. Davis, M. Iwanami, I. K. Stamos, and K. Takahashi, *J. Org. Chem.* **37**, 1111 (1972).

¹⁸⁷ D. C. Dittmer, K. Ikura, J. M. Balquist, and N. Takashina, *J. Org. Chem.* **37**, 225 (1972).

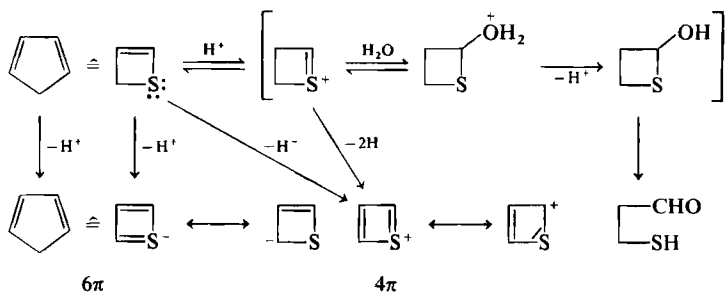
¹⁸⁸ D. C. Dittmer, P. L. F. Chang, F. A. Davis, M. Iwanami, I. K. Stamos, and K. Takahashi, *J. Org. Chem.* **37**, 1116 (1972).

All thietes are thermally unstable because of the strained C—S bond, which may easily lead to ring opening. This makes all thietes highly reactive. The least stable representative is the fused thiete–cyclohexane ring system (149), which may decompose explosively even at room temperature.^{186–188}

2,4-Diphenylthiete 1,1-dioxides (mp 137–138°C) decompose via electrocyclic ring opening to a vinyl sulfene intermediate that instantly undergoes desulfinylation to product 222. The intermediate could be successfully trapped as the corresponding sulfonic acid (Eq. 60).¹⁰ Thiete can be considered



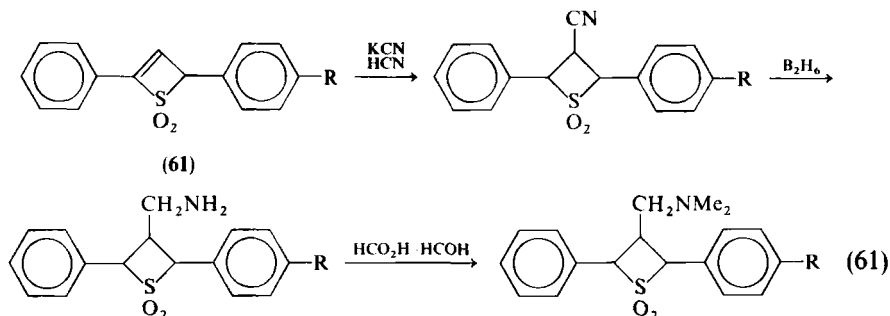
to be the heterocyclic analog of cyclopentadiene because sulfur has the same electronegativity as carbon. When one double bond in the five-membered ring is exchanged with the sulfur atom, the π conjugation remains intact.¹⁸⁶



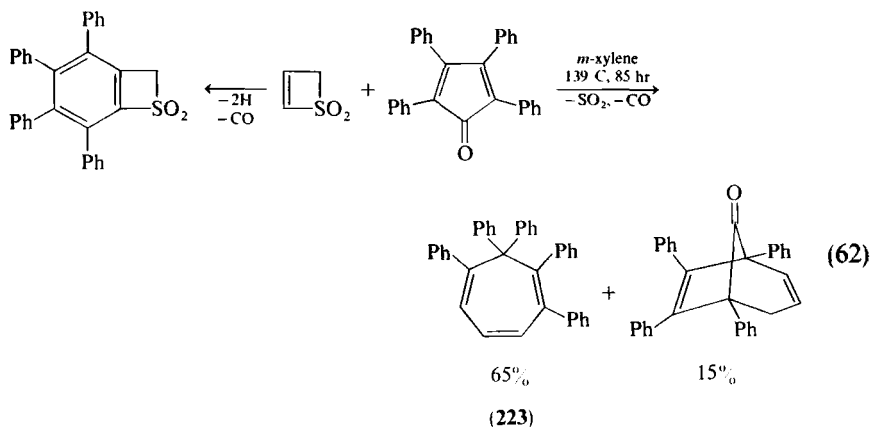
An interesting feature is the ability to form a 6π -electron anion that is isoelectronic with the cyclopentadienyl ion. The cation that is produced by hydride subtraction contains a 4π -electron system.

2. Addition and Cycloaddition

The susceptibility of the thiete 1,1-dioxides to nucleophilic addition reactions can be utilized to produce 3-substituted thietane derivatives. For example, the thus easily attainable 3-cyano and 3-nitroalkyl-substituted derivatives could be reduced to the 3-aminomethylthietanes^{10,189} (Eq. 61).

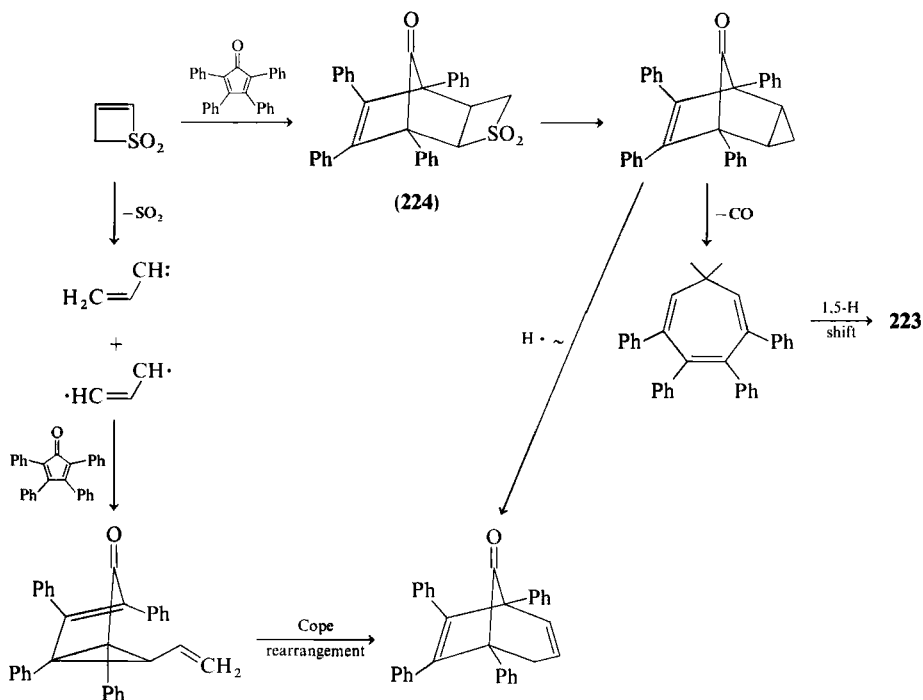


Thiete sulfones show an irregular behavior pattern when involved in cycloaddition reactions. With 1,3-dienes, dienamines, enamines, ynamines, diazoalkenes, cyclopropadiene, and its substitution products, furan, and anthracene, the addition proceeds in the normal fashion. With certain Diels–Alder reagents such as tetraphenylcyclopentadienone (tetracyclone), however, the cyclic sulfones react anomalously.¹⁸⁷ The Diels–Alder adducts undergo decomposition with SO₂ and CO extrusion to a seven-membered ring, the tetraphenylcycloheptatriene **223**. Bicyclic octadienone is produced as well (Eq. 62). The mechanism of this unusual reaction is proposed by

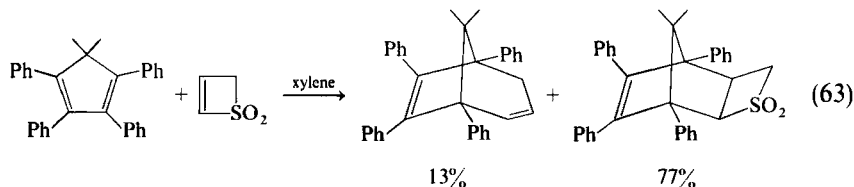


¹⁸⁹ J. E. Coates and F. S. Abbott, *J. Org. Chem.* **42**, 3506 (1977).

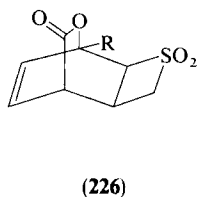
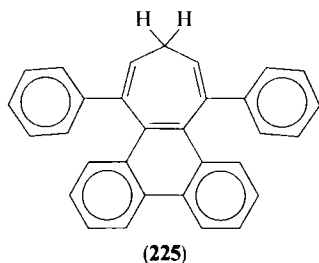
Dittmer *et al.* to be as shown in Scheme 13. The final product **223** resulting from intermediate **224** via CO expulsion and subsequent proton rearrangement is more likely than the reverse-reaction sequence. Thiete 1,1-dioxide



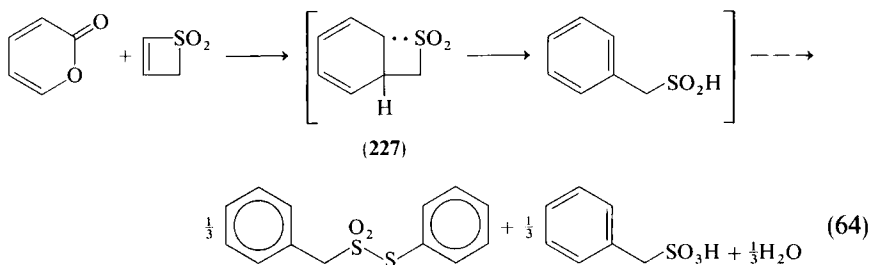
reacts with other dienes in a similar manner, which opens up new prospects



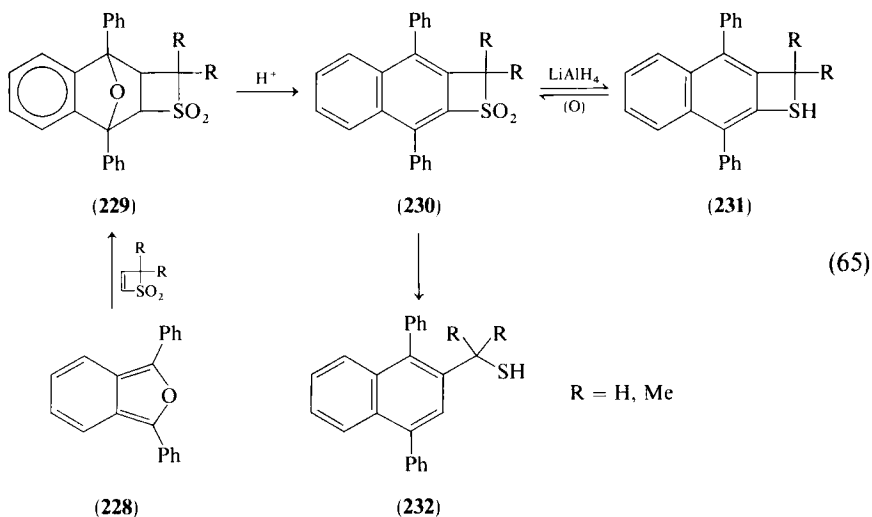
in preparatory organic chemistry (Eq. 63). With 1,3-diphenyl-2H-cyclopenta-phenanthrene-2-one (**225**) (phencyclone) the reaction resulted in **226**.



α -Pyrone, often used as a reactive diene in Diels-Alder reactions, reacts with thiete sulfone in like manner (Eq. 64). The intermediates are also Diels-Alder adducts, such as **226**, that easily give off CO_2 to form **227**. Stable

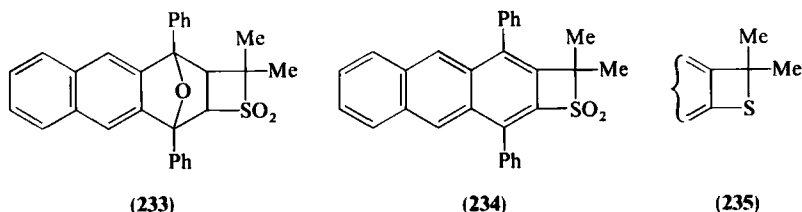


Diels-Alder adducts **229** were produced by the interaction of thiete sulfone and **228** (Eq. 65).¹⁹⁰ Acid hydrolysis leads to product **230**, reduction either

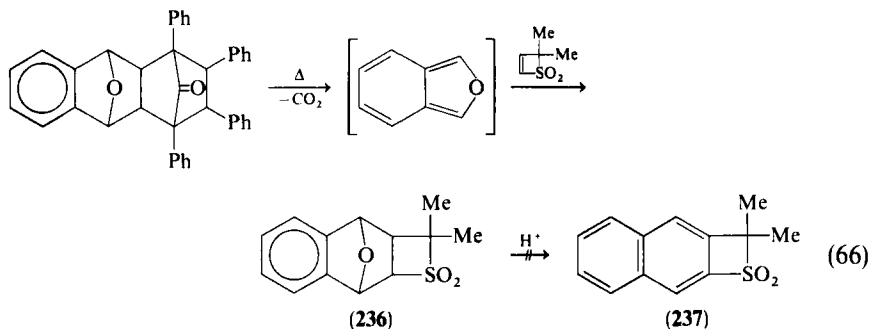


¹⁹⁰ L. A. Paquette, *J. Org. Chem.* **30**, 629 (1965).

to thietane **231** or to thiol **232**. In like manner, the products **233**, **234**, and **235** have been synthesized. In one case the Diels–Alder adduct remained



resistant to acid hydrolysis (Eq. 66).



Benzothiete sulfone, when treated with LiAlH_4 and H_3O^+ , did not lead to the product corresponding to **232** but rather to *o*-toluenethiol.¹³⁸

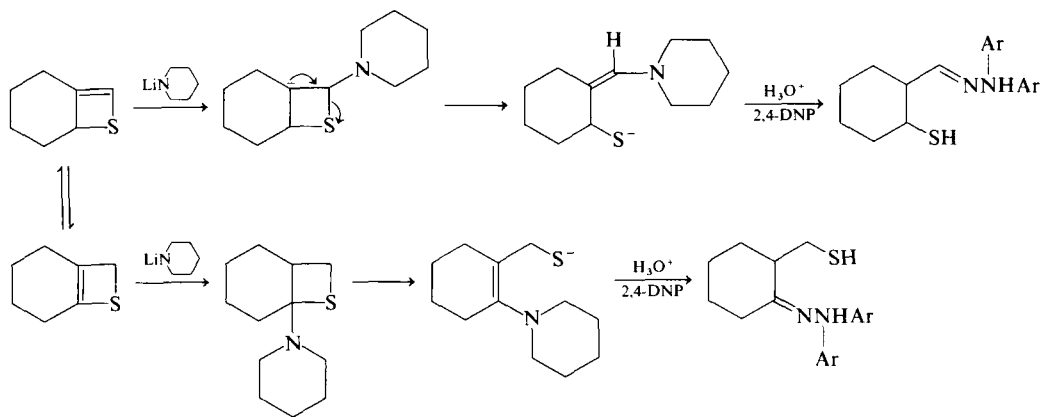
3. Ring Opening

Reaction of thiete and its fused derivatives with alkylolithium and alkylpotassium bases leads to the opening of the ring via two different modes of cleavage.¹⁸⁶ (Scheme 14)

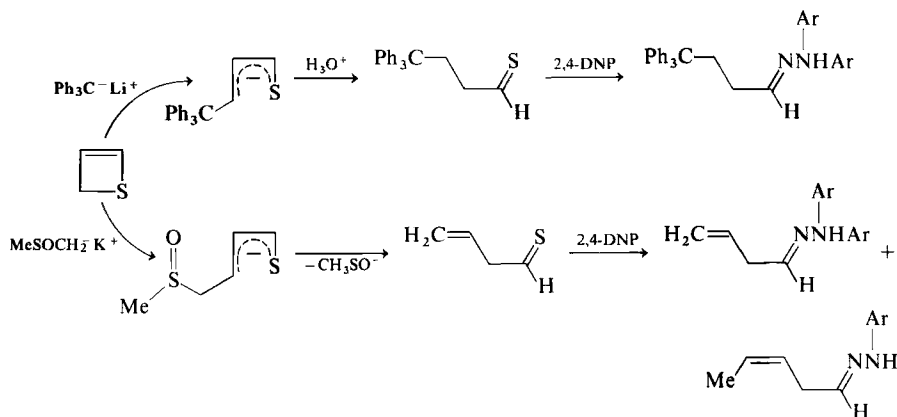
Thiete can undergo a ring-opening reaction with trityllithium or potassium mesylate (Scheme 15).

Fused thietes often show a different chemical behavior than the thietes themselves. The fused thiete undergoes ring opening much more readily because of greater ring strain, and thus the reaction with 2,4-dinitrophenylhydrazine takes a different course⁴³ (Schemes 15 and 16).

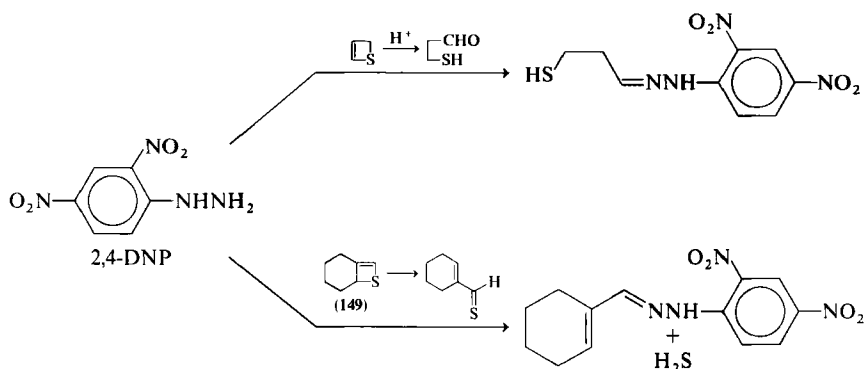
The ring opening of **149** proceeds much faster than the protonation of the double bond. With thiete as a more stable compound, the opposite condition



SCHEME 14

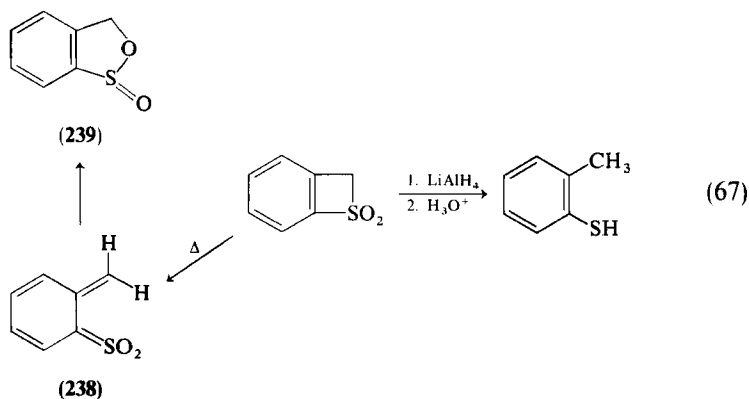


SCHEME 15



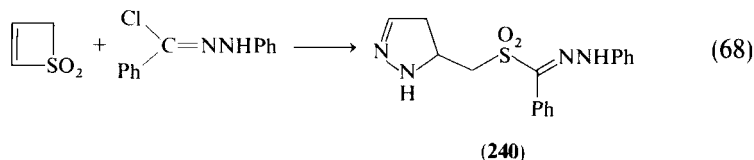
SCHEME 16

is true. Thermolysis of the benzothiete 1,1-dioxide leads via intermediate **238** to the ring-enlarged structure **239**^{1,38} (Eq. 67).



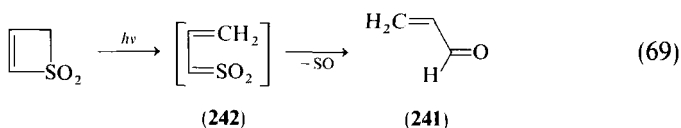
4. Ring Expansion

The treatment of thiete sulfone with substituted ketimines in triethylamine yielded the ring-enlargement product **240**¹⁹¹ (Eq. 68).

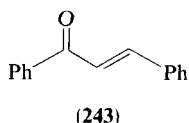


5. Photochemistry

Irradiation of a thiete 1,1-dioxide in degassed solutions of acetonitrile or dichloromethane at 253 nm leads to the formation of vinyl ketones (**241**) via

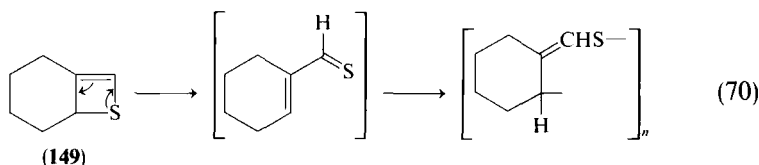


ring opening of the intermediate acyclic sulfone **242** with subsequent extrusion of sulfur monoxide⁴² (Eq. 69). In the case of 2,4-diphenylthiete 1,1-dioxide, a benzylideneacetophenone (chalcone) is produced (**243**).



6. Polymerization

Thietes are easily polymerized to different types of macromolecules that often turn up as undesired by-products. The fused compound **149** is easily transformed into a thioacrolein (Eq. 70), which polymerizes to a glassy solid.¹⁸⁶



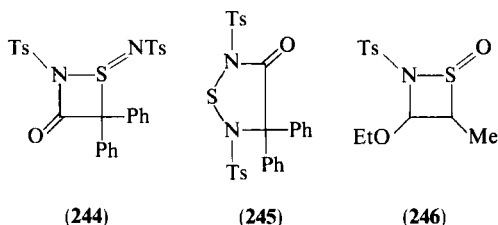
¹⁹¹ P. Della Croce, P. Del Buttero, S. Maiorana, and R. Vistocco, *J. Heterocycles Chem.* **15**, 515 (1978).

C THIAZETIDINES AND THIAZETES

1. *Thermally and Chemically Induced Ring-Opening Reactions*

The most studied reactions of the thiazetidines are the thermolytic decomposition and conversion reactions. 1,2-Thiazetidines are more unstable than the 1,3-thiazetidines because of the lone-pair-lone-pair repulsion of the N—S bond. Oxidation of the sulfur atom or appropriate substitution on the nitrogen atom have a stabilizing effect on the ring structure.

Thermolysis of most thiazetidines by themselves leads to ring opening. If heating takes place with another reagent, ring enlargement to another heterocyclic system ensues, as discussed in Section V,D. The decomposition products derived from thermolytic treatment are listed in Table I. In the case of **244**, heating to 70°C leads to the isomerization product **245**.¹⁴⁵ Often the mode of thermal fragmentation is used to study the stereochemistry of a specific reaction.^{54,141} By heating the *cis* product **246** to 65°C, cycloreversion to the original vinyl ether and the *N*-sulfinylsulfonamide derivative proceeded with over 90% stereospecificity to the *cis* fragment.³⁷

2. *Polymerization*

Initial ring-opening reactions of thiazetidines can directly lead to polymeric material (Eq. 71).⁷⁷ The polymer **247** is a yellow substance with a net formula of $(\text{H}_2\text{S}_2\text{C}_2\text{N}_2)_n$.

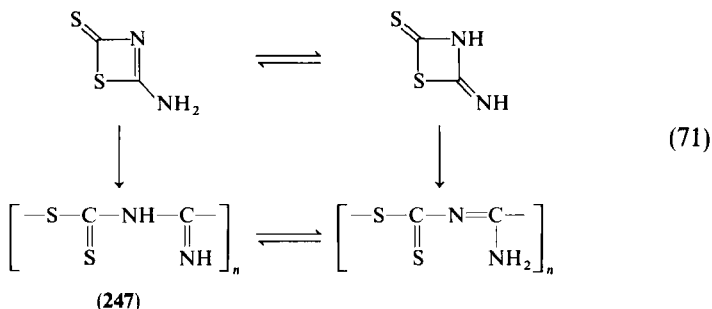
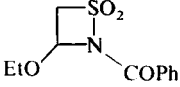
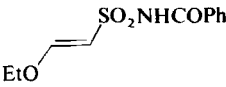
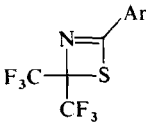
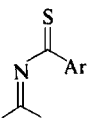
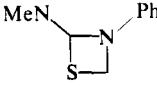
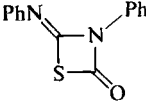
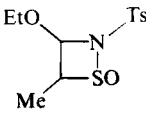
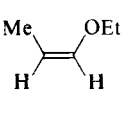
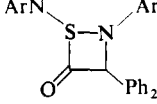
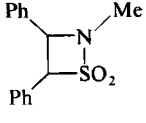
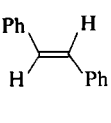
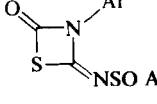


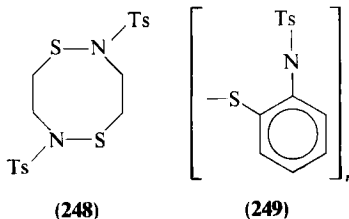
TABLE I
PRODUCTS FROM THE THERMOLYSIS OF THIAZETIDINES

Thiazetidine	Product(s)	References
		149
		155
	MeN=C=NPh, CH ₂ S, CH ₃ NCS, PhN=CH ₂	199
	PhN=C=NPh, COS	152
		137
	ArNCO, S ArN=CHPh ₂	54, 141
		142
	ArSO ₂ N=C=NAr ArNCO, ArSO ₂ NCS	152

Ring-opening polymerization of 1,2-thiazetidines, because of their highly strained ring structure, is often investigated for eventual technological applications. Imai *et al.* have produced a new class of polyamide-polysulfonamide, using this technique. 4,4-Dimethyl-1,2-thiazetidin-3-one 1,1-dioxide

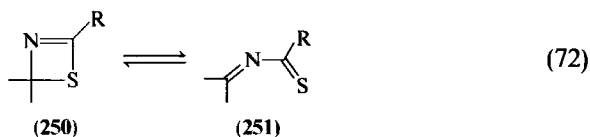
was polymerized by potassium fluoride catalysis with the help of initiators.¹⁹²⁻¹⁹⁵

Whereas *N*-tosyl-1,2-thiazetidine undergoes dimerization to **248** in order to lessen ring strain, the corresponding benzothiazetidine derivative is known to polymerize to **249**.¹⁶



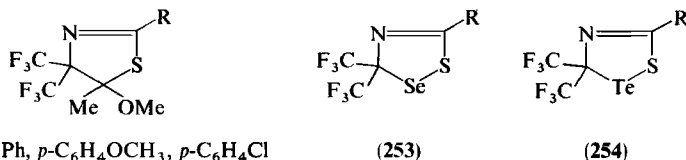
3. Ring Expansion

A thermal equilibrium exists between the 1,3-thiazetes **250** and the hetero-1,3-dienes **251**, which makes the latter compounds readily available for the synthesis of novel S-heterocycles (Eq. 72).^{49,196,197}



The heating of the 1,3-thiazetes **250** in xylene at 140°C leads to the formation of **252**.¹⁹⁶ Heating the same compound with P₂Se₃ produced the selenium-containing heterocycle **253**.¹⁹⁸

Thermolysis of **250** with Sb₂Te₃ in toluene for 4–5 weeks in the dark at 80–90°C gave the 1,2,4-thiatellurazolines **254**. When **250** was heated with



¹⁹² Y. Imai, H. Hirnkaw, K. Okuyama, and M. Ueda, *Makromol. Chem.* **180**, 1413 (1979).

¹⁹³ Y. Imai, M. Ueda, and K. Okuyama, *Makromol. Chem.* **179**, 2327 (1978).

¹⁹⁴ Y. Imai, M. Ueda, and K. Okuyama, *Polym. J.* **10**, 637 (1978).

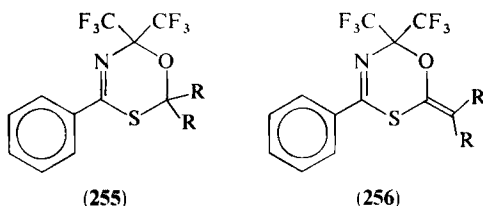
¹⁹⁵ Y. Imai, H. Hirnkaw, K. Okuyama, and M. Ueda, *Makromol. Chem.* **180**, 25 (1979).

¹⁹⁶ K. Burger and R. Ottlinger, *Chem.-Ztg.* **101**, 402 (1977).

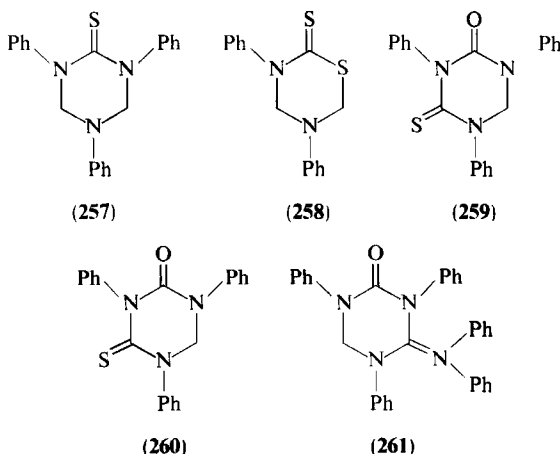
¹⁹⁷ K. Burger, R. Ottlinger, and J. Albanberger, *Chem. Ber.* **110**, 2114 (1977).

¹⁹⁸ K. Burger and R. Ottlinger, *J. Fluorine Chem.* **29**, 11 (1978).

ketones, the oxathiazine **255** was formed; when treated with ketenes, the same heterocycles carrying an exocyclic double bond were produced (**256**).⁴⁹

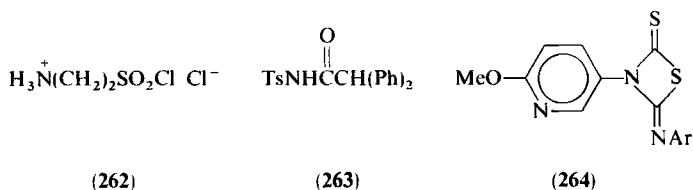


Thermal treatment of **250** with phenyl isothiocyanate at 160–170°C produced the triazine **257** and the thiadiazine **258**. Reaction with phenyl isocyanate at 166°C led to the different triazine derivatives **259**, **260**, and **261**.¹⁹⁹



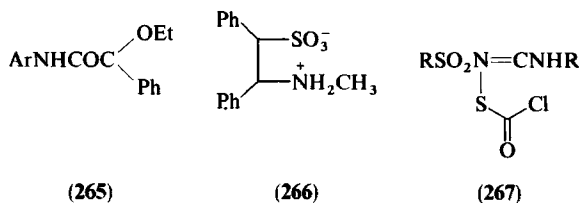
4. Solvolysis

Acid hydrolysis of thiazetidine 1,1-dioxide causes ring opening to the salt **262**.⁵⁵ Hydrolysis of **244** produces the ring-opened structure **263**.¹⁴⁵ Treatment of **264** with ethanol leads to thiourethane and substituted ureas.⁶⁶



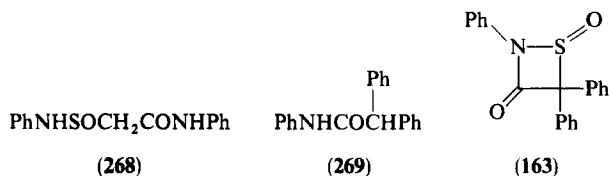
¹⁹⁹ W. Ried and O. Möisinger, *Justus Liebigs Ann. Chem.*, 1661 (1977).

When **176** is treated with hydrochloric acid it gives the intermediate acyclic structure **265**, which decomposes to sulfonyl isothiocyanates, isothiocyanates, and chlorformamidines.¹⁵⁴ Solvolysis of **155** with ethanol, followed by addition of hydrogen bromide, leads to **266**.¹⁴¹ Base hydrolysis of **156** leads to the zwitterionic structure **267**.¹⁴¹



5. Reaction with Specific Reagents

The thiazetidine **163** has been specifically synthesized to give the opening structure **268** after treatment with aniline in acetone at -78°C .¹⁴⁶ 1,2-Thiazetidines (**172**) have been treated with Grignard reagents to yield sulfonamide sulfoxides.¹⁵⁰



6. Oxidation and Reduction

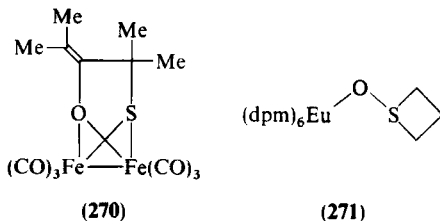
Reduction of **155** by Raney nickel produced the ring-opened structure **269**.¹⁴¹ Oxidation of the same compound with *m*-chloroperbenzoic acid resulted in the formation of the thiazetidine 1-oxide **163**.

D. FORMATION OF METAL COMPLEXES

In several cases thietane derivatives have been used as ligands in organo-metallic compounds. Stable enolate complexes have been derived from tetramethyl-3-thietanone and diiron nonacarbonyl.²⁰⁰ Both compounds were heated in *n*-hexane at 60°C in an argon atmosphere for longer periods of

²⁰⁰ B. Czanderna, K. H. Jogun, J. J. Stezowski, and B. Föhlich, *J. Am. Chem. Soc.* **98**, 6696 (1976).

time during which 3 molar equivalents of carbon monoxide were liberated. The resulting product consisted of dark red crystals with a melting point of 78–80°C. The structure of the diiron hexacarbonyl complex was resolved to be **270**. The same product could be prepared by photolysis of iron pentacarbonyl and the thietanone at 35°C (253.7 nm argon) with good yields.



The very useful lanthanide shift reagents, which facilitate analysis of molecular stereochemistry because of their line-broadening characteristics in NMR spectra, were studied when bound as a chelate complex to thietanes. X-Ray analysis of the adduct 3,3-dimethylthietane 1-oxide with tris(dipivalomethanato)europium(III) [Eu(dpm)₃] revealed the structure of a seven-coordinate complex (**271**).^{201,202}

As highly reactive heterocycles, the thietes are well suited for the formation of metal complexes. Takahashi and Dittmer both individually and in collaboration have been involved with the interaction of thietes and iron or cobalt carbonyls. During the thermally or photochemically induced complexation process, ring opening takes place so that the resultant thioacrolein is the actual ligand in the organometallic compound (Scheme 17).^{43,203,204}

X-Ray analysis of the red-orange crystalline thioacrolein complex **272**, which is derived from the dimeric thioacrolein derivative by way of thermal elimination of carbon monoxide (Scheme 17), has revealed a structure with an essentially square Fe₂S₃ array. Analogous reactions with iron carbonyls have been carried out by McCaskie *et al.*²⁰⁵ who used thiete 1,1-dioxide instead of thiete (Scheme 18).

An unusual behavior of the thiete sulfone was noticed when it was refluxed together with complex **273** under nitrogen in olefin-free hexane. When the same conditions are applied to thiete 1,1-dioxide alone, the heterocyclic ring remains intact.

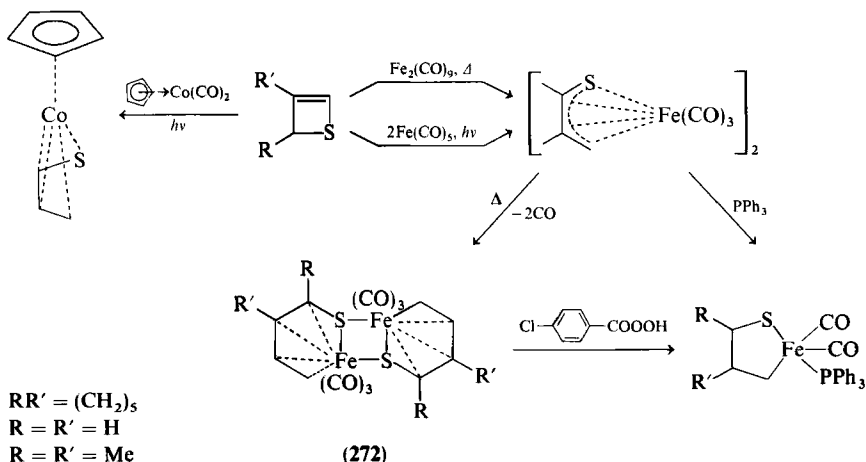
²⁰¹ J. Uebel and R. M. Wing, *J. Am. Chem. Soc.* **94**, 8910 (1972).

²⁰² W. Harrack, *J. Am. Chem. Soc.* **93**, 6800 (1971).

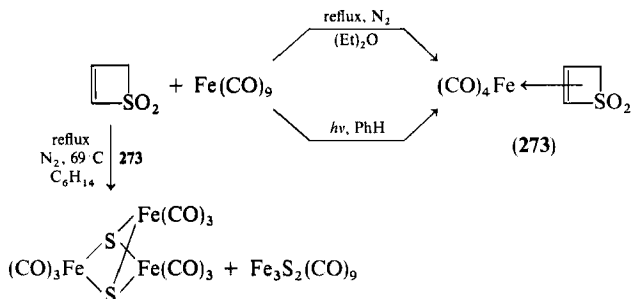
²⁰³ K. Takahashi and M. Iwanami, *J. Am. Chem. Soc.* **95**, 6113 (1973).

²⁰⁴ D. C. Dittmer, K. Takahashi, M. Iwanami, A. I. Tsai, P. L. Cho, B. B. Blidner, and I. Stamp, *J. Am. Chem. Soc.* **98**, 2795 (1976).

²⁰⁵ J. E. McCaskie, P. L. Chang, T. R. Nelsen, and D. C. Dittmer *J. Org. Chem.* **38**, 3963 (1973).

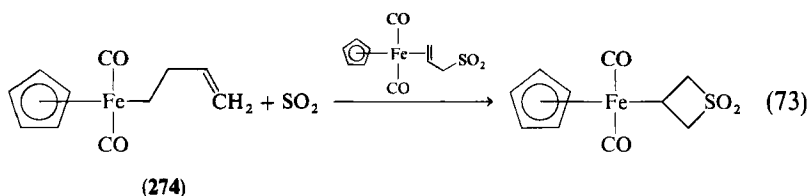


SCHEME 17

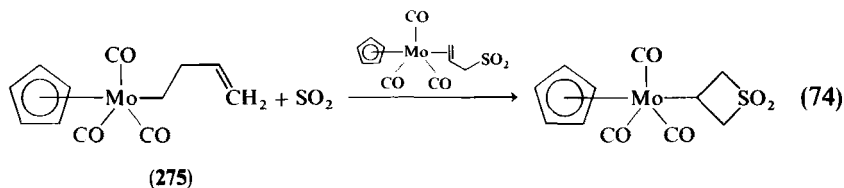


SCHEME 18

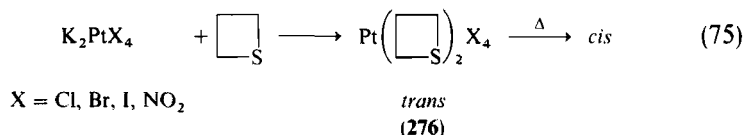
The treatment of cyclopentadienyl-metal-2-alkenyl carbonyl complexes, such as **274** and **275**, with SO_2 leads to the formation of thietane 1,1-dioxide as ligand (Eqs. 73 and 74).²⁰⁶ Thietane and platinum(II) have also been found



²⁰⁶ L. S. Chen, S. R. Su, and A. Wojcicki, *Inorg. Chim. Acta* **27**, 79 (1978).



to join in coordination compounds (Eq. 75) of the type **276**.²⁰⁷ The structures could easily be ascertained by ¹⁹F-NMR spectroscopy.



A selection of different derivatives prepared by the method of direct sulfonation of α -olefins are listed in Table II.

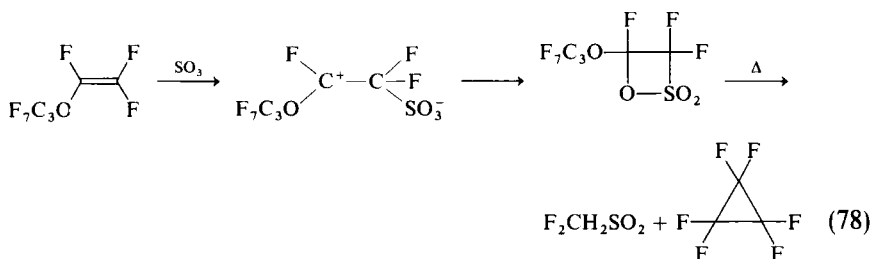
TABLE II
PRODUCTS (R) FROM THE SULFONATION OF ALKENES

Reagents	$\begin{array}{c} \text{R}^2 \quad \text{R}^3 \\ \quad \\ \text{R}^1 - \text{C} - \text{C} - \text{R}^4 \\ \\ \text{O} - \text{SO}_2 \\ \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 \end{array}$	$\begin{array}{c} \text{R}^2 \quad \text{R}^3 \\ \quad \\ \text{R}^1 - \text{C} - \text{C} - \text{R}^4 \\ \\ \text{O} - \text{SO}_2 \\ \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 \end{array}$	References
$\text{CF}_2=\text{CF}_2, \text{SO}_3$	F, F, F, F	—	211
$\text{CF}_3\text{CF}=\text{CF}_2, \text{SO}_3$	F, F, F, CF_3	—	219
$\text{CFCl}=\text{CFOR}, \text{SO}_3$ R = Me, Et	F, Cl, OR, F	—	211
$\text{CF}_3=\text{CFOCF}_3, \text{SO}_3$	OC_3F_7 , F, F, F	—	213
$\text{CF}_2=\text{CFCF}_2-\text{CF}_2, \text{SO}_2-\text{P}_2\text{O}_5$	—	F, F, $\text{CF}=\text{CF}_2$, F	213a
$\text{CF}_2=\text{C}(\text{CF}_3)\text{OEt}, \text{SO}_2, 20-0^\circ\text{C}$	CF_3 , OEt, F, F	—	213
$\text{RCH}=\text{CH}_2, \text{SO}_3$ (air) R* = $\text{C}_{15}-\text{C}_{18}$ chains	R*, H, H, H	—	216

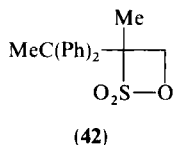
²⁰⁷ Y. N. Kukushkin, E. A. Andronov, and V. P. Yustratow, *Zh. Neorg. Khim.* **23**, 3062 (1978).

proved very successful in the preparation of various β -sultones and β -sultines.²¹⁰⁻²¹²

Much research has been done on the synthesis of perhalogenated β -sultones. The sulfonation of acyclic fluorovinyl ethers leads to a product that is stable up to slightly above room temperature. Thermolysis decomposes the ring structure under SO_2 evolution and formation of acid fluorides and perfluorocyclopropane²¹³ (Eq. 78). β -Sultones have been synthesized by addition of sulfonyl chlorides to perhalogenated ketones in the presence of triethylamine. The formation of the 1-oxa-2-thiacyclobutane 2,2-dioxides appears to require an activated but sterically unhindered carbonyl group because acetone, chloroacetone, trifluoroacetophenone, and *p*-nitroacetophenone did not yield the desired products.⁵⁷



The reaction of concentrated sulfuric acid with 2,2-dimethyl-1,1-diphenylpropan-1-ol produced in high yield the β -sultone **42**.⁶⁸



The reaction of methanesulfonyl chloride $\text{CH}_3\text{SO}_2\text{Cl}$ (to generate in situ the reactive sulfene $\text{CH}_2=\text{SO}_2$) with chloral in triethylamine produced a β -sultone bearing a trichloromethyl group at position 3.^{214,215} Sultones

²¹⁰ M. Nagayama, O. Okumura, S. Noda, and A. Mori, *Chem. Commun.*, 841 (1973).

²¹¹ M. A. Belaventsev, L. L. Mikheev, V. M. Pavlov, G. A. Sokolskii, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **21**, 2441 (1972).

²¹² F. Pueschel and D. Drescher, German (East) Patent 81996 (1971).

²¹³ C. G. Krespan and B. E. Smart, *J. Am. Chem. Soc.* **99**, 1214 (1977).

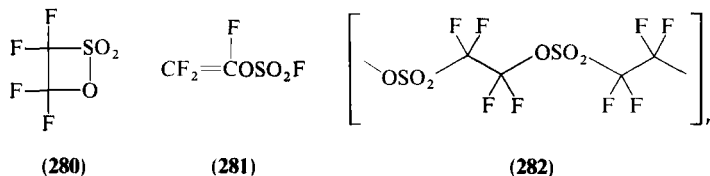
^{213a} N. B. Kaz'mina, I. C. Knunyants, E. I. Mysov, and G. M. Kuz'yants, *Izv. Akad. Nauk SSSR, Ser. Khim.* No. 1, 163 (1978).

²¹⁴ D. Borrmann and R. Wegler, *Chem. Ber.* **99**, 1245 (1966).

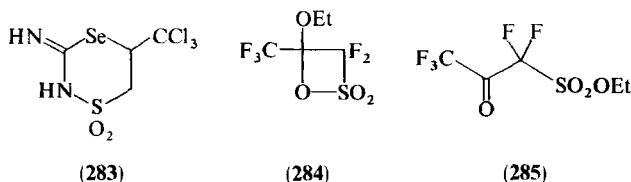
²¹⁵ F. I. L. Luknickij and B. A. Vovsi, *Dokl. Akad. Nauk SSSR* **172**, 1327 (1967).

often occur as cyclic intermediates during the formation of aliphatic products as is shown in the oxidation of polychloroethylene with SO_3 .²¹⁶

Knunjanec and co-workers^{217,218} have researched the ring-opening reactions of perfluorinated derivatives of β -sultones. The treatment with various sulfones lead to a whole series of novel, saturated, and unsaturated halogenated sultone derivatives. Hydrolysis with H_2O , bases, or acids has led to a variety of aliphatic structures.^{219,220} The perfluorinated β -sultone **280** is not a very stable compound. After a month's storage in sealed tubes it undergoes isomerization to the acyclic trifluorovinyl fluorosulfate **281**.²²¹ Sokol'skij and Knunjanec²²² noticed the quantitative polymerization of **280** at -70°C to **282**.



An interesting seleno derivative in 42% yield can be obtained by treating 3-trichloromethyl β -sultone with selenoethylurea in triethylamine²¹⁵ (**283**). At 25°C the compound **284** undergoes rearrangement to the open structure **285**.²¹³



Thermolysis of β -sultines leads via retrocycloaddition to the fragmentation products SO_2 and olefin.²²³ The fragmentation is stereospecific in accordance with orbital symmetry principles.

²¹⁶ D. M. Marquis, S. H. Sherman, R. House, and W. A. Sweeney, *J. Am. Oil Chem. Soc.* **43**, 607 (1966).

²¹⁷ G. A. Sokol'skij and I. L. Knunjanec, *Izv. Akad. Nauk SSSR* **9**, 1655 (1965).

²¹⁸ I. L. Knunjanec, G. A. Sokol'skij, and M. A. Belavencev, *Izv. Akad. Nauk SSSR* **6**, 1017 (1922).

²¹⁹ R. E. Banks, G. M. Haslam, R. N. Haszeldine, and A. Peppin, *J. Chem. Soc. C* **13**, 1171 (1966).

²²⁰ L. I. Ragulin, P. P. Ropalo, C. A. Sokol'skij, and I. L. Knunjanec, *Izv. Akad. Nauk SSSR* **8**, 1754 (1967).

²²¹ M. A. Belavencev, G. A. Sokol'skij, and I. L. Knunjanec, *Izv. Akad. Nauk SSSR, Ser. Khim.* No. 1613 (1965).

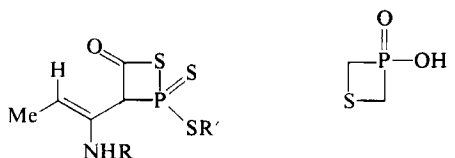
²²² G. A. Sokol'skij and I. L. Knunjanec, *Izv. Akad. Nauk SSSR* No. 6, 1289 (1967).

²²³ L. Carlsen and J. P. Snyder, *Tetrahedron Lett.* **23**, 2045 (1977).

VIII. Synthesis and Reactions of Thiaphosphetanes, Silathietanes, and Selenathietanes

Of the possible four-membered sulfur-containing heterocyclic rings that contain another heteroatom, which is not sulfur, oxygen, or nitrogen, only the thiaphosphetanes, silathietanes, and selenathietanes are discussed in the literature up to 1980.

Thiaphosphetan-4-ones (**286**) have been described.



(286) R, R' = Me, Me; Me, Et; or Pr, Et (287)

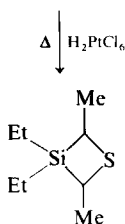
Thiaphosphetane chemistry, long neglected, is being investigated. Both the 1,2- and the 1,3-thiaphosphetanes have been synthesized and derived. The structure **287** was prepared by Soviet chemists²²⁴⁻²²⁶ in 1969 and 1970. Schmidt and Hamblin¹⁸ have produced a variety of ammonium salts of the phosphathietanes that they have patented as effective lubricants, (see **23** in Section II).

Silathietanes were first introduced as a new heterocyclic system in 1976 by a Soviet research group²²⁷ who prepared them by addition of substituted silanes to divinyl sulfide (Scheme 19). The two possible intermediates **288**



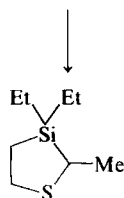
(288)

(289)



(290)

R = H, Et



(291)

SCHEME 19

²²⁴ N. V. Ivasyuk and I. M. Shermergorn, *Bull. Acad. Sci. USSR*, 436 (1969).

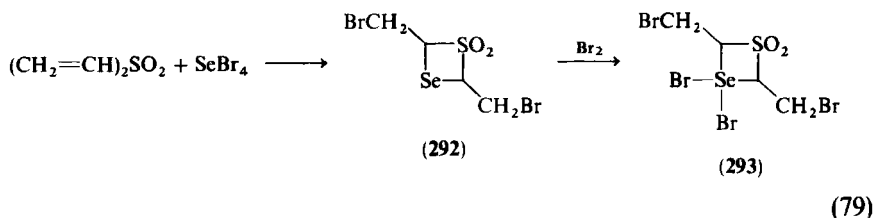
²²⁵ N. V. Ivasyuk and I. M. Shermergorn, *Izv. Akad. Nauk SSSR, Ser. Khim.* No. 2, 481 (1969).

²²⁶ M. M. Gilyazov, T. A. Zyablikova, E. K. Mukhametzyanov, and I. M. Shermergorn, *Izv. Akad. Nauk SSSR, Ser. Khim.* No. 5, 1177 (1970).

²²⁷ M. G. Voronkov, T. D. Barton, S. V. Kirpichanko, V. V. Keiki, and V. A. Pestunovich, *Tezisy Dokl. Nauchn. Sess. Khim. Tekhnol. Org. Soedin. Sery Sernistykh Neftel*, 14th, 1975, 710 (1976).

and **289** each led to a novel four- and five-membered ring (compounds **290** and **291**, respectively). The cis-trans isomers originated in a 1:1 ratio.

Selenathietanes also were first prepared by a Soviet research group in 1978.²²⁸ By treating diethylene sulfone with selenium bromide (Eq. 79) the brominated selenathietanone **292** was formed; it could be further brominated to **293**.



Note Added in Proof

We wish to append a few additional references that have been found since this article was written. They are cross-referenced here by relevant sections.

II. Occurrence and Uses

Veterinary repellent²²⁹

III. Structural and Physical Properties

Ab initio one-electron property calculations. II Molecular oxetane, cyclobutanone, and thietane.²³⁰

Preparation of stable β -sultines. Crystal structure of 2,2-bis(*p*-fluorophenyl)-3,3-dimethyl-1,2-oxathietan 2-oxide.²³¹

The crystal and molecular structure of *trans*-2,2-diphenyl-3,4-dichlorothietane.²³²

²²⁸ Y. V. Migalina, V. G. Lend'el, A. Z. Koz'min, and N. S. Zefiror, *Khim. Geterosikl. Soedin.*, 708 (1978).

²²⁹ A. Alscher, C. Birkner, W. Dietrich, and H. Schildknecht, Ger. Offen. 3030760 (1982).

²³⁰ G. De Brouckere and R. Broer, *Mol. Phys.* **43**, 1139 (1981).

²³¹ M. D. M. Gray, D. R. Russell, D. J. H. Smith, T. Durst, and B. Gimbarzevsky, *J. C. S. Perkin I*, 1826 (1981).

²³² S. Kumakura, *Bull. Chem. Soc. Jpn.* **54**, 3701 (1981).

Structure of 1,3-dimethyl-3'',4'-diphenylimidazolidine-2-spiro-2'(2'*H*)thiete-4,5-dione.²³³

Cyclization of γ,δ -unsaturated sulfenic acids to give thietan 1-oxide derivatives. Crystal structure of *rel*-(1*R*,2*S*,3*R*,4*R*)-3-hexyl-2-hydroxy-methyl-4-methylthietan 1-oxide.²³⁴

IV. Spectroscopic Investigations

The stereochemistry of bis(imino)thiazetidines.²³⁵

Photoelectron spectroscopy of sulfur heterocycles adsorbed onto a copper (110) surface.²³⁶

Gas-phase reactions. Thioacrolein: most stable C₃H₄S isomer and its PE spectroscopic gas-phase detection.²³⁷

A. Ultraviolet-Visible Spectra

Electric dichroism spectroscopy in the vacuum ultraviolet. Thietane, tetrahydrothiophene, and tetrahydrothiopyran.²³⁸

C. Nuclear Magnetic Resonance

Conformational study of 3-substituted thietane 1-oxides. Lanthanide shift reagent approach.²³⁹

V. Preparation

A. Thietanes

Formation of 3-thietanones out of α,α' -dibromoketones and sodium hydrogen sulfide and their ring-opening reactions.²⁴⁰

A convenient synthesis of 2,4-diarylthietanes by reductive cyclization of *O,O*-diethyl *S*-1,3-diaryl-3-oxopropylphosphorodithioates.²⁴¹

Concerning the structure of the reaction products from *N*-sulfinyl-sulfonamides and dimethylketen-*N*-phenylimine.²⁴²

²³³ H. Gotthardt, and O. M. Huss, *Acta Crystallogr.*, Sect. B, **38**, 875 (1982).

²³⁴ D. N. Jones, T. P. Kogan, P. Murray-Rust, J. Murray-Rust, and R. F. Newton, *J. C. S. Perkin I*, 1325 (1982).

²³⁵ G. L'Abbé, L. van Meervelt, G. S. D. King, *Bull. Soc. Chim. Belg.* **90**, 1185 (1981).

²³⁶ T. M. Thomas, F. A. Grimm, T. A. Carlson, and P. A. Agron, *J. Electron Spectrosc. Relat. Phenom.* **25**, 159 (1982).

²³⁷ H. Bock, S. Mohmand, T. Hirabayashi, and A. Semkow, *Chem. Ber.* **115**, 1339 (1982).

²³⁸ D. D. Altenloh, and B. R. Russell, *J. Phys. Chem.* **86**, 1960 (1982).

²³⁹ D. J. H. Smith, J. D. Finlay, C. R. Hall, and J. J. Uebel, *J. Org. Chem.* **44**, 4757 (1979).

²⁴⁰ B. Föhlisch and W. Gottstein, *Liebigs Ann. Chem.* **11**, 1768 (1979).

²⁴¹ Y. Ueno, L. D. S. Yadav, and M. Okawara, *Synthesis*, **7**, 547 (1981).

²⁴² G. L'Abbé, A. Van Asch, J.-P. Dekerk, and T. Minami, *Tetrahedron Lett.* **22**, 583 (1981).

Reaction of α -dialkylaminostyrenes and 2-(α -dimethylaminovinyl)-thiophen with sulfene. Simple thermolysis of 3-phenyl-3-dimethylaminothietan 1,1-dioxide.²⁴³

Preparation and reactions of novel cyclic β -oxosulfonium salts obtained by the acid-induced cyclization of 1-diazo- ω -phenylthio-2-alkanones.²⁴⁴

Synthesis of thietan-2,4-dithiones.²⁴⁵

Lack of stereoselectivity in the formation of thietane 1,1-dioxide derivatives from anancomeric aminocyclohexenes.²⁴⁶

Synthesis of strained heterobicycles from alkynes and heterocumulenes.²⁴⁷

Sulfotrioxidation of perfluoroisopropylalkenyl ethers.²⁴⁸

B. Thietes

Chemistry of *N*-sulfonyl-substituted thiiranimines.²⁴⁹

Electrophilic attack on a metal alkynyl by carbon disulfide. Thiete derivative is used as an intermediate.²⁵⁰

C. Thiazetidines

λ^6 -Thiadiazetidione.²⁵¹

A novel isothiocyanate dimer.²⁵²

Four-membered ring adducts from $2\pi + 2\pi$ cycloaddition of ketenimines to sulfur dioxide. Isolation of 1,2-thiazetid-3-one 1-oxides.²⁵³

β -Sultames. Simple method for synthesis of substituted 1,2-thiazetid-1,1-dioxide.²⁵⁴

Synthesis and properties of β -sultams.²⁵⁵

²⁴³ L. N. Koikov, P. B. Terent'ev, and N. S. Kulikov, *Zh. Org. Khim.* **17**, 1087 (1981).

²⁴⁴ W. T. Flowers, A. M. Freitas, G. Holt, and S. C. Purkiss, *J. C. S. Perkin I*, 1119 (1981).

²⁴⁵ M. Muraoka, T. Itoi, and T. Yamamoto, *J. Chem. Res., Synop.* **9**, 256 (1982).

²⁴⁶ P. Bradamante, M. Forchiassin, G. Pitacco, C. Russo, and E. Valentin, *J. Heterocycl. Chem.* **19**, 985 (1982).

²⁴⁷ H. Hogeveen, R. F. Kingma, and D. M. Kok, *J. Org. Chem.* **47**, 1909 (1982).

²⁴⁸ V. F. Sherstkov, S. R. Sterlin, L. S. German, and I. L. Knunyants, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **12**, 2796 (1982).

²⁴⁹ G. L'Abbé, J. P. Dekerk, C. Martens, and S. Toppet, *J. Org. Chem.* **45**, 4366 (1980).

²⁵⁰ J. P. Selegue, *J. Am. Chem. Soc.* **104**, 119 (1982).

²⁵¹ F.-M. Tesky and R. Mews, *Chem. Ber.* **113**, 2434 (1980).

²⁵² K. E. Fahrenholtz, W. Benz, J. F. Blount, and T. H. Williams, *J. Org. Chem.* **45**, 4219 (1980).

²⁵³ A. Dondoni, P. Giorgianni, A. Battaglia, and G. D. Andreotti, *J. Chem. Soc. Chem. Commun.*, **7**, 350 (1981).

²⁵⁴ E. Meyle, and H.-H. Otto, *Arch. Pharm. (Weinheim, Ger.)* **316**, 281 (1983).

²⁵⁵ W. Koller, A. Linkies, H. Rehling, and D. Reuschling, *Tetrahedron Lett.* **24**, 2131 (1983).

VI. Chemical Properties and Reactions

A. Thietanes

Cationic polymerization of thietanes initiated by trityl salts: mechanism of the initiation reaction.²⁵⁶

Syntheses of "thiiranoradialenes" from a 3-thietanone derivative.²⁵⁷

Transformation of 2-methylthiacyclobutane in the presence of aluminum oxide.²⁵⁸

Wittig condensation of a thietan-2-one with stabilized phosphoranes.²⁵⁹

²⁵⁶ S. M. Florquin, and E. J. Goethals, *Makromol. Chem.* **182**, 3371 (1981).

²⁵⁷ W. Ando, Y. Haniu, and T. Takata, *Tetrahedron Lett.* **22**, 4815 (1981).

²⁵⁸ A. K. Yus'kovich, *et al.*, *Khim. Geterotsikl. Soedin.* **2**, 184 (1982).

²⁵⁹ S. Al-Zaidi and R. J. Stoodley, *J. Chem. Soc. Chem. Commun.* **17**, 995 (1982).

The Bipyridines

LINDSAY A. SUMMERS

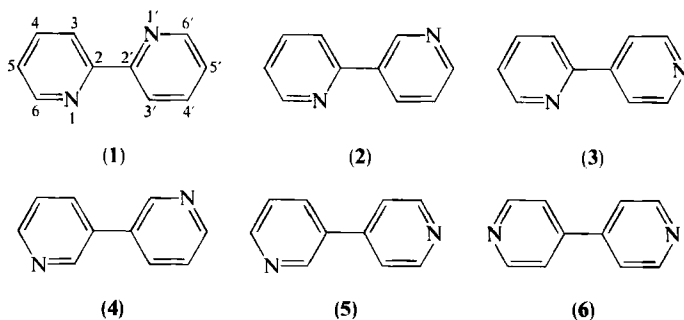
*Department of Chemistry, University of Newcastle,
New South Wales, Australia*

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I. Introduction

There are six bipyridines whose structures are 2,2'-1, 2,3'-2, 2,4'-3, 3,3'-4, 3,4'-5, and 4,4'-6. The term *bipyridine* is in accord with current *Chemical Abstracts* nomenclature, although the compounds have also been named as bipyridyls and dipyridyls.



The organic chemistry of the bipyridines has not previously been reviewed, although short sections devoted to aspects of bipyridines are included in treatises on pyridine chemistry.¹⁻³ A booklet on some aspects of bipyridines has appeared in Russian.⁴ This review provides a thorough coverage of the chemistry of the bipyridines to the end of 1981 and includes work reported in most chemical journals to mid-1982. The early chemistry of the bipyridines, which has received some discussion in the reviews of pyridine chemistry, is mentioned briefly to provide continuity. The review excludes the extensive metal and nonmetal coordination chemistry of the bipyridines

¹ H. S. Mosher, *Heterocycl. Comp.* **1**, 500-504 (1950).

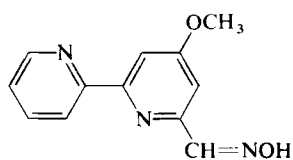
² L. E. Tenenbaum, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Part 2, pp. 224-231. Wiley (Interscience), New York, 1961.

³ R. G. Micetich, in "Pyridine and Its Derivatives" (R. A. Abramovitch, ed.), Suppl., Part 2, pp. 373-377. Wiley (Interscience), New York, 1974.

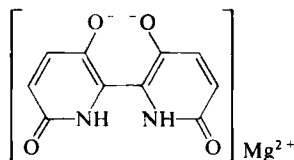
⁴ N. N. Mel'nikov, E. G. Novikov, and B. A. Khaskin, "Chemistry and Biological Activity of Dipyridyls and Their Derivatives." Khimiya, Moscow, 1975.

but, for the sake of completeness, gives reference to the review literature on these topics.

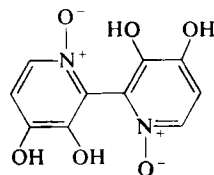
Apart from 3,4'-bipyridine, which was not fully authenticated until 1950, all of the parent bipyridines were synthesized for the first time many years ago (see Section III). Several bipyridines occur naturally. 2,2'-Bipyridine has been reported to be present in crude oil.⁵ The simple substituted 2,2'-bipyridine, named caeruleomycin (7), is an antibiotic isolated from *Streptomyces caeruleus*.^{6,7} Closely related analogs have recently been isolated from the same microorganism.⁸ A blue bacterial pigment from *Arthrobacter nicotinovorum* probably has structure 8,^{9,10} whereas the principal toxin orellanine (9) of the mushroom *Cortinarius orellanus* is a derivative of 2,2'-bipyridine 1,1'-dioxide.¹¹ It is light sensitive.¹² 2,3'-Bipyridine is reported to occur in seedlings of tobacco (*Nicotiana* species),^{13,14} and 5-methyl-2,3'-bipyridine has been isolated from a tobacco extract.¹⁵ The terpyridine nicotelline (10) is a minor tobacco alkaloid.¹⁶⁻¹⁸ The analogous structure, where the central ring is fully reduced, has also been isolated from *Nicotiana tabacum*.¹⁹ 2,3'-Bipyridine and nemertelline (11) have been found to be neurotoxins isolated from the marine hoplonemertine worm *Amphiporus angulatus*.²⁰



(7)



(8)



(9)

⁵ L. N. Tokareva, G. D. Gal'pern, A. V. Kotova, and I. D. Leonov, *Neftekhimiya* **7**, 790 (1967) [*CA* **68**, 41918 (1968)].

⁶ P. V. Divekar, G. Read, and L. C. Vining, *Can. J. Chem.* **45**, 1215 (1967).

⁷ S. Ranganathan, B. B. Singh, and P. V. Divekar, *Can. J. Chem.* **47**, 165 (1969).

⁸ A. G. McInnes, D. G. Smith, J. L. C. Wright, and L. C. Vining, *Can. J. Chem.* **55**, 4159 (1977).

⁹ H. Neimur, H. Bucherer, H. J. Zeitler, and E. Stadler, *Hoppe-Seyler's Z. Physiol. Chem.* **337**, 282 (1964).

¹⁰ H. Neimur, H. Bucherer, H. J. Zeitler, and E. Stadler, *Arch. Mikrobiol.* **54**, 56 (1966).

¹¹ W. Z. Antkowiak and W. P. Gessner, *Tetrahedron Lett.*, 1931 (1979).

¹² H. Kuernsteiner and M. Moser, *Mycopathologia* **74**, 65 (1981).

¹³ M. Y. Lovkova, G. S. Il'in, and N. S. Minozhedinova, *Prikl. Biokhim. Mikrobiol.* **6**, 481 (1970) [*CA* **73**, 127917 (1970)].

¹⁴ V. S. Vasinev, *Stud. Nauchn. Rab., Univ. Druzhby Nar.* **15**, 108 (1970) [*CA* **75**, 72704 (1971)].

¹⁵ A. H. Warfield, W. D. Galloway, and A. G. Kallianos, *Phytochemistry* **11**, 3371 (1972).

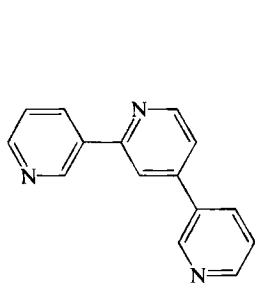
¹⁶ F. Kuffner and N. Faderl, *Monatsh. Chem.* **87**, 71 (1956).

¹⁷ F. Kuffner and E. Kaiser, *Monatsh. Chem.* **85**, 896 (1954).

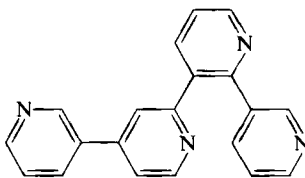
¹⁸ J. Thesing and A. Muller, *Angew. Chem.* **68**, 577 (1956).

¹⁹ T. Kisaki, S. Mizusaki, and E. Tamaki, *Phytochemistry* **7**, 323 (1968).

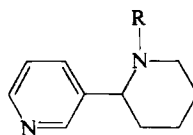
²⁰ W. R. Kem, K. N. Scott, and J. H. Duncan, *Experientia* **32**, 684 (1976).



(10)



(11)



(12)

Although discussion of the chemistry and biochemistry of pyridylpiperidines, bipiperidines, and related reduced bipyridines is outside the scope of a review on bipyridines, it is necessary for the understanding of subsequent sections of this review to record the structures of reduced 2,3'-bipyridines that occur naturally. Several compounds of this type are important alkaloids isolated from several plant species, notably, *Anabasis*, *Duboisia*, *Mackinlaya*, *Marsdenia*, *Nicotiana*, and *Priesteya*. Anabasine (also known as neonicotine) has structure 12 ($R = H$),²¹⁻²⁹ and is insecticidal.³⁰ The closely related structures 1-methylanabasine (12: $R = CH_3$),^{31,32} anatabine (13: $R = H$),³³⁻³⁶ its 1-methyl derivative (13: $R = CH_3$),^{32,35} anabaseine (14),³⁷ and anabasamine (15)^{38,39} also occur naturally in plant material. Anabaseine is also a toxin

²¹ A. Orekhov and G. Men'shikov, *Ber. Dtsch. Chem. Ges. B* **64**, 266 (1931).

²² M. Ehrenstein, *Arch. Pharm. (Weinheim, Ger.)* **269**, 627 (1931).

²³ C. R. Smith, *J. Am. Chem. Soc.* **57**, 959 (1935).

²⁴ E. Spath and L. Mamoli, *Ber. Dtsch. Chem. Ges. B* **69**, 1082 (1936).

²⁵ P. I. Mortimer and S. Wilkinson, *J. Chem. Soc.*, 3967 (1957).

²⁶ P. I. Mortimer, *Aust. J. Sci.* **20**, 87 (1957).

²⁷ J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. H. Redcliffe, *Aust. J. Chem.* **19**, 151 (1966).

²⁸ E. Steinegger, E. Schlunegger, F. Schnyder, and R. Frehner, *Pharm. Weekbl.* **106**, 245 (1971).

²⁹ R. E. Summons, J. Ellis, and E. Gellert, *Phytochemistry* **11**, 3335 (1972).

³⁰ E. J. Seiferle and D. E. H. Frear, *Ind. Eng. Chem.* **40**, 683 (1948).

³¹ C. R. Smith, *J. Am. Chem. Soc.* **54**, 397 (1932).

³² E. Spath and F. Keszler, *Ber. Dtsch. Chem. Ges. B* **70**, 2450 (1937).

³³ E. Spath and F. Keszler, *Ber. Dtsch. Chem. Ges. B* **70**, 239 (1937).

³⁴ E. Spath and F. Keszler, *Ber. Dtsch. Chem. Ges. B* **70**, 704 (1937).

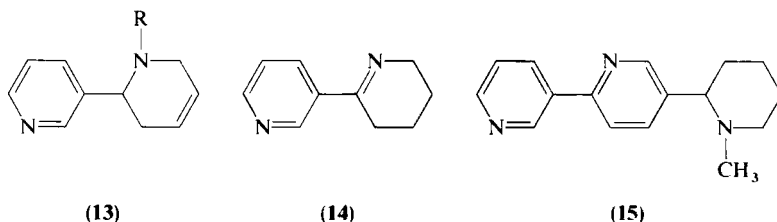
³⁵ P. M. Quan, T. K. B. Karns, and L. D. Quin, *Chem. Ind. (London)*, 1553 (1964).

³⁶ E. Leete, *J. C. S. Chem. Commun.*, 9 (1975).

³⁷ T. Kisaki and E. Tamaki, *Phytochemistry* **5**, 293 (1966).

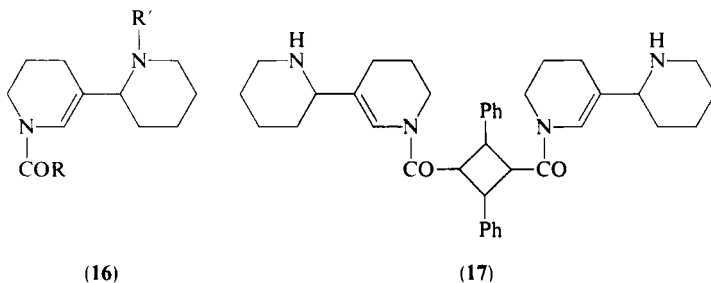
³⁸ A. S. Sadykov, S. Z. Mukhamedzhanov, and K. A. Aslanov, *Dokl. Akad. Nauk Uzb. SSR* **24**, 34 (1967) [*CA* **68**, 78473 (1968)].

³⁹ S. Z. Mukhamedzhanov, K. A. Aslanov, A. S. Sadykov, V. B. Leont'ev, and V. K. Kiryukhin, *Khim. Prir. Soedin.* **4**, 158 (1968) [*CA* **69**, 87277 (1968)].



found in the nemertean flatworm *Paranemertes*.^{40,41} It also occurs in the marine worm *Amphiporus angulatus*²⁰ and is a poison-gland product in *Aphaenogaster* ants.⁴²

Several derivatives of 2,3'-bipyridine, where both rings are reduced, are also alkaloids present, for example, in *Adenocarpus*, *Ammodendron*, *Astrocasia*, *Coelidium*, *Genista*, *Liparia*, *Lupinus*, and *Retama* species. Ammodendrine has structure 16 ($R = \text{CH}_3$, $R' = \text{H}$),⁴³⁻⁵² isorensine has structure 16 ($R = \text{cis-CH=CHPh}$, $R' = \text{H}$),⁵³⁻⁵⁷ adenocarpine and its racemic form



⁴⁰ W. R. Kem, B. C. Abbott, and R. M. Coates, *Toxicon* **9**, 15 (1971).

⁴¹ W. R. Kem, *Toxicon* **9**, 23 (1971).

⁴² J. W. Wheeler, O. Olubajo, C. B. Storm, and R. M. Duffield, *Science* **211**, 1051 (1981).

⁴³ A. P. Orekhov, N. Proskurnina, and G. Lazurevskii, *Ber. Dtsch. Chem. Ges. B*, **68**, 1807 (1935).

⁴⁴ A. Orekhoff and N. Proskournina, *Bull. Soc. Chim. Fr.* **5**, 29 (1938).

⁴⁵ C. Schopf and F. Braun, *Naturwissenschaften* **36**, 377 (1949).

⁴⁶ I. Ribas and J. Vega, *Ion* **13**, 148 (1953).

⁴⁷ J. Dominguez, I. Ribas, and J. Vega, *An. R. Soc. Espan. Fis. Quim., Ser. B* **52**, 43 (1956).

⁴⁸ C. Schopf, F. Braun, and K. Kreibich, *Justus Liebigs Ann. Chem.* **674**, 87 (1964).

⁴⁹ E. Steinegger and K. Wicky, *Pharm. Acta Helv.* **40**, 610 (1965).

⁵⁰ E. Steinegger and C. Moser, *Pharm. Acta Helv.* **42**, 177 (1967).

⁵¹ R. R. Arndt and L. M. Du Plessis, *J. S. Afr. Chem. Inst.* **21**, 54 (1968).

⁵² E. Steinegger and E. Schlunegger, *Pharm. Acta Helv.* **45**, 369 (1970).

⁵³ M. R. Mendez and I. Ribas, *An. R. Soc. Espan. Fis. Quim., Ser. B* **54**, 161 (1958).

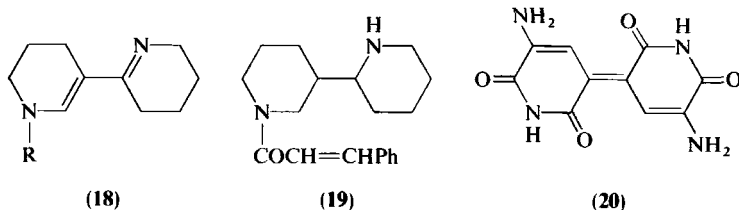
⁵⁴ I. Ribas and M. Diago, *An. R. Soc. Espan. Fis. Quim., Ser. B* **55**, 83 (1959).

⁵⁵ C. Schopf and W. Merkel, *Naturwissenschaften* **53**, 274 (1966).

⁵⁶ C. Schopf and W. Merkel, *Justus Liebigs Ann. Chem.* **701**, 180 (1967).

⁵⁷ R. Bernasconi and E. Steinegger, *Pharm. Acta Helv.* **45**, 42 (1970).

orensine have structure **16** ($R = \text{trans-CH=CHPh}$, $R' = \text{H}$),^{53,57-63} whereas santiaguine has structure **17**.^{53,57,58,64-66} 1-Methylammodendrine (**16**: $R = R' = \text{CH}_3$),⁶⁷ hystrine (**18**: $R = \text{H}$),^{68,69} 1'-acetylhystrine (**18**: $R = \text{COCH}_3$),⁶⁷ and astrophylline (**19**)⁷⁰ have also been isolated from plant material.



Not surprisingly, therefore, 2,3'-bipyridine is an ingredient of tobacco smoke and is a constituent of tobacco liquors.⁷¹⁻⁷³ An alkaloid named isonicotine, which was isolated from Turkish tobacco liquors and was thought to be a pyridylpyrrole derivative,⁷⁴ was subsequently shown to be identical to 2,3'-bipyridine.⁷⁵ 5-Methyl-2,3'-bipyridine,⁷⁶ 2,2'-bipyridine,^{77,78} and 4,4'-bipyridine⁷⁶ are also found in tobacco smoke. The range of bipyridines found in tobacco smoke condensate has been considerably extended with the identification of several alkyl substituted 2,2'-, 2,3'-, and 3,3'-bipyri-

⁵⁸ I. Ribas and Pastor Taladrid, *Monit. Farm. Ter.* **56**, 377 (1950) [*CA* **45**, 1303 (1951)].

⁵⁹ I. Ribas, R. Guitian, and Pastor Taladrid, *An. R. Soc. Espan. Fis. Quim., Ser. B* **47**, 715 (1951).

⁶⁰ A. G. Gonzalez, A. Calero, and M. Muñoz, *An. R. Soc. Espan. Fis. Quim., Ser. B* **47**, 730 (1951).

⁶¹ J. Vega, J. Dominguez, and I. Ribas, *An. R. Soc. Espan. Fis. Quim., Ser. B* **50**, 89 (1954).

⁶² C. Schopf and K. Kreibich, *Naturwissenschaften* **41**, 335 (1954).

⁶³ I. Ribas and M. R. Mendez, *An. R. Soc. Espan. Fis. Quim., Ser. B* **51**, 55 (1955).

⁶⁴ L. Costa and I. Ribas, *An. R. Soc. Espan. Fis. Quim., Ser. B* **48**, 699 (1952).

⁶⁵ J. Dominguez, M. R. Mendez, and I. Ribas, *An. R. Soc. Espan. Fis. Quim., Ser. B* **52**, 133 (1956).

⁶⁶ I. Ribas and M. Ribas, *An. R. Soc. Espan. Fis. Quim., Ser. B* **62**, 845 (1966).

⁶⁷ W. L. Fitch, P. M. Dolinger, and C. Djerassi, *J. Org. Chem.* **39**, 2974 (1974).

⁶⁸ E. Steinegger, C. Moser, and P. Weber, *Phytochemistry* **7**, 849 (1968).

⁶⁹ E. Steinegger and P. Weber, *Helv. Chim. Acta* **51**, 206 (1968).

⁷⁰ H. A. Lloyd, *Tetrahedron Lett.*, 4537 (1965).

⁷¹ W. G. Frankenburg, A. M. Gottscho, E. W. Mayaud, and T. C. Tso, *J. Am. Chem. Soc.* **74**, 4309 (1952).

⁷² R. N. Jeffrey and T. C. Tso, *J. Agric. Food Chem.* **3**, 680 (1955).

⁷³ L. D. Quin, *J. Org. Chem.* **24**, 914 (1959).

⁷⁴ E. Noga, *Fachliche Mitt. Oesterr. Tabakregie*, Nos. 1 and 2 (1914) [*CA* **9**, 1769 (1915)].

⁷⁵ E. Spath and S. Biniecki, *Ber. Dtsch. Chem. Ges. B* **72**, 1809 (1939).

⁷⁶ Y. Saint-John and P. Moree-Testa, *J. Chromatogr.* **198**, 188 (1980).

⁷⁷ I. Schmeltz, A. Wenger, D. Hoffmann, and T. C. Tso, *J. Agric. Food Chem.* **27**, 602 (1979).

⁷⁸ E. V. Brown and I. Ahmad, *Phytochemistry* **11**, 3485 (1972).

dines.⁷⁹ Other 3,3'-bipyridine derivatives have been found to be natural products. The blue bacterial dye indigoidine has structure **20**⁸⁰⁻⁸² and a blue pigment from *Corynebacterium insidiosum* is closely related in structure to **20** (Table I).⁸³

TABLE I
SOME PROPERTIES OF THE BIPYRIDINES

Bipyridine	Melting point (°C)	Boiling point ^a	Dissociation constants ^b	
			pK ₁	pK ₂
2,2'	69.5 ⁸⁴⁻⁸⁶	272-273 ⁸⁵	4.25 ⁹⁸	-0.15 ¹⁰⁶
	70 ⁸⁷	272.5 ⁸⁴	4.3 ^{99,100}	-0.2 ^{98,103}
	71-72 ⁸⁸	273-275 ⁸⁷	4.35 ¹⁰¹	-0.5 ^{107,108}
			4.4 ^{102,103}	
			4.5 ¹⁰⁴	
2,3'	Oil	294-295 ⁹⁵	4.4 ¹⁰²	1.5 ¹⁰²
		295-296 ⁷⁵		
		298 ⁹⁶		
2,4'	58 ⁸⁶	145-155/11 mm ⁸⁹	4.8 ¹⁰²	1.2 ¹⁰²
	58-59 ⁸⁹	148-150/11 mm ⁹¹		
	61.5 ^{90,91}			
3,3'	64-66 ⁹²	300-301 ⁹⁶	4.6 ¹⁰²	3.0 ¹⁰²
	67-68 ⁸⁵	291-292/736 mm ⁹⁷		
		190-192/25 mm ⁹²		
3,4'	Oil ⁹⁰	150-155/11 mm ⁸⁹	4.85 ¹⁰²	3.0 ¹⁰²
4,4'	112 ^{c86,93}	305 ⁹⁴	4.8 ¹⁰²	3.2 ^{102,105,109}
	114 ^{c94}	293/744 mm ⁹⁴	4.9 ¹⁰⁵	
	73 ^{d93,94}			

^a At about 760 mm unless stated otherwise.

^b At about 25°C.

^c Anhydrous.

^d Dihydrate.

⁷⁹ R. A. Heckman and F. W. Best, *Tob. Int.* **183**, 83 (1981).

⁸⁰ R. Kuhn, H. Bauer, and H. J. Knackmuss, *Chem. Ber.* **98**, 2139 (1965).

⁸¹ R. Kuhn, M. R. Starr, D. A. Kuhn, H. Bauer, and H. J. Knackmuss, *Arch. Mikrobiol.* **51**, 71 (1965).

⁸² H. Bauer and G. Pfeiffer, *Chem.-Ztg.* **100**, 373 (1976).

⁸³ R. Kuhn, W. Blau, H. Bauer, H. J. Knackmuss, D. A. Kuhn, and M. P. Starr, *Naturwissenschaften* **51**, 194 (1964).

⁸⁴ F. Blau, *Monatsh. Chem.* **10**, 375 (1889).

⁸⁵ G. T. Morgan and F. H. Burstall, *J. Chem. Soc.*, 20 (1932).

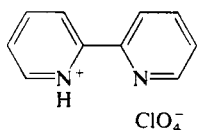
II. Physical Properties

A. CRYSTAL STRUCTURE

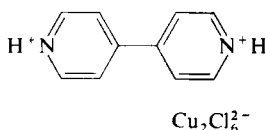
Most of the crystal structure work on the parent bipyridines has been concerned with 2,2'-bipyridine. Optical properties of crystalline 2,2'-bipyridine have been studied.^{110,111} High resolution X-ray diffraction analysis and other studies with 2,2'-bipyridine have shown that the rings are coplanar with the nitrogen atoms in an anti position with respect to the bond joining the rings. The molecule has a center of symmetry,¹¹²⁻¹¹⁵ and the bond lengths in the rings agree well with the values for pyridine. The length of the bond between the pyridine rings is 1.50 Å, which is slightly greater than the length of 1.48 Å for the similar bond between the rings of biphenyl. The bond angles in the rings correspond to those of a slightly distorted hexagon. The

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- ⁸⁶ C. W. N. Cumper, R. F. A. Ginman, and A. I. Vogel, *J. Chem. Soc.*, 1188 (1962).
⁸⁷ J. P. Wibaut and J. Overhoff, *Recl. Trav. Chim. Pays-Bas* **47**, 761 (1928).
⁸⁸ F. Hein and H. Schwedler, *Ber. Dtsch. Chem. Ges. B* **68**, 681 (1935).
⁸⁹ F. Kuffner and F. Straberger, *Monatsh. Chem.* **88**, 793 (1957).
⁹⁰ P. Krumholz, *J. Am. Chem. Soc.* **73**, 4449 (1951).
⁹¹ R. F. Homer, *J. Chem. Soc.*, 1574 (1958).
⁹² M. I. Kabachnik and V. V. Reson, *J. App. Chem. USSR (Engl. Transl.)* **9**, 2026 (1936) [CA **31**, 2608 (1937)].
⁹³ J. P. Wibaut and E. Dingemanse, *Recl. Trav. Chim. Pays-Bas* **42**, 240 (1923).
⁹⁴ H. Weidel and M. Russo, *Monatsh. Chem.* **3**, 850 (1882).
⁹⁵ A. Orekhov and G. Menshikov, *Ber. Dtsch. Chem. Ges. B* **65**, 232 (1932).
⁹⁶ C. R. Smith, *J. Am. Chem. Soc.* **52**, 397 (1930).
⁹⁷ Z. H. Skraup and G. Vortmann, *Monatsh. Chem.* **4**, 570 (1883).
⁹⁸ R. H. Linnell and A. Kaczmarczyk, *J. Phys. Chem.* **65**, 1196 (1961).
⁹⁹ J. H. Baxendale and P. George, *Trans. Faraday Soc.* **46**, 55 (1950).
¹⁰⁰ T. R. Harkins and H. Freiser, *J. Am. Chem. Soc.* **77**, 1374 (1955).
¹⁰¹ R. Nasanen, *Suom. Kemistil. B* **28**, 161 (1955) [CA **50**, 8299 (1956)].
¹⁰² P. Krumholz, *J. Am. Chem. Soc.* **73**, 3487 (1951).
¹⁰³ H. H. Perkampus and H. Kohler, *Z. Elektrochem.* **64**, 365 (1960).
¹⁰⁴ B. R. James and R. J. P. Williams, *J. Chem. Soc.*, 2007 (1961).
¹⁰⁵ T. R. Musgrave and C. E. Mattson, *Inorg. Chem.* **7**, 1433 (1968).
¹⁰⁶ P. Krumholz, *J. Phys. Chem.* **60**, 87 (1956).
¹⁰⁷ F. H. Westheimer and O. T. Benfey, *J. Am. Chem. Soc.* **78**, 5309 (1956).
¹⁰⁸ W. A. E. McBryde, *Can. J. Chem.* **43**, 3472 (1965).
¹⁰⁹ D. K. Lavalley and E. B. Fleischer, *J. Am. Chem. Soc.* **94**, 2583 (1972).
¹¹⁰ W. M. D. Bryant, *J. Am. Chem. Soc.* **63**, 511 (1941).
¹¹¹ J. Mitchell, *Anal. Chem.* **21**, 448 (1949).
¹¹² F. W. Cagle, *Acta Crystallogr.* **1**, 158 (1948).
¹¹³ A. M. Liquori and A. Ripamonti, *Ric. Sci.* **26**, 1442 (1956) [CA **51**, 846 (1957)].
¹¹⁴ L. L. Merritt and E. D. Schroeder, *Acta Crystallogr.* **9**, 801 (1956).
¹¹⁵ F. Bertinotti, A. M. Liquori, and R. Pirisi, *Gazz. Chim. Ital.* **86**, 893 (1956).

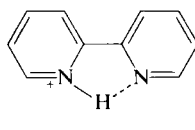
molecules in the crystal unit cell show no unusually close approaches. This indicates that the only forces between the molecules in the crystal are weak Van der Waal's forces. This is consistent with the low melting point ($\sim 70^\circ\text{C}$) of 2,2'-bipyridine and with the tendency of the crystals to sublime slowly at room temperature. During the formation of metal complexes, the rings of 2,2'-bipyridine are rotated so that the nitrogen atoms are in an eclipsed position. Numerous X-ray studies of complexes of 2,2'-bipyridine¹¹⁶ and of 2,2':6',2''-terpyridine¹¹⁷ have been determined. Interestingly, X-ray diffraction analysis of 2,2'-bipyridinium perchlorate (**21**) has shown that the structure consists of discrete perchlorate and 2,2'-bipyridinium ions.¹¹⁸ The cation is not strictly planar but has an axially distorted cisoid conformation. The dihedral angle between the pyridyl and pyridinium rings is 16.6° . 2,2'-Bipyridinium bis(fluorosulfonate), however, where both nitrogens are protonated, has recently been shown to have a transoid conformation with an angle of distortion of 31.5° from the ideal transoid conformation.¹¹⁹ In the iodine complexes 2,2'-bipyridine \cdot 2ICl and 2,2'-bipyridine \cdot 2IBr, the two pyridine rings are significantly twisted with respect to one another and the molecules are not planar.¹²⁰



(21)



(22)



(23)

Although the high resolution X-ray crystal analysis of 4,4'-bipyridine has not been reported, the crystal structure of 4,4'-bipyridinium chlorocuprate (**22**) has been discussed. Whereas the dimensions of the 4,4'-bipyridinium dication may have been distorted because of the influence of the bulky metal cation, it is interesting to note that the 4,4'-bipyridinium dication is planar with both pyridine rings lying in the same plane.¹²¹ In metal complexes of the parent 4,4'-bipyridine, however, the pyridine rings may be coplanar¹²² or rotated up to 40° with respect to one other.¹²³

¹¹⁶ For example, G. A. Barclay, B. F. Hoskins, and C. H. L. Kennard, *J. Chem. Soc.*, 5691 (1963).

¹¹⁷ For example, D. J. Robinson and C. H. L. Kennard, *Aust. J. Chem.* **19**, 1285 (1966).

¹¹⁸ J. Lipkowski, P. Sgarabotto, and G. D. Andreotti, *Cryst. Struct. Commun.* **5**, 931 (1976).

¹¹⁹ C. Belin, J. Roziere, and J. Potier, *Acta Crystallogr., Sect. B* **B37**, 1306 (1981).

¹²⁰ S. Soled and G. B. Carpenter, *Acta Crystallogr., Sect. B* **B30**, 910 (1974).

¹²¹ M. Bukowska-Strzyzewska and A. Tosik, *Pol. J. Chem.* **53**, 2423 (1979).

¹²² F. Kubel and J. Strahle, *Z. Naturforsch., B: Anorg. Chem. Org. Chem.* **B37**, 272 (1982).

¹²³ F. S. Stephens and R. S. Vagg, *Inorg. Chim. Acta* **42**, 139 (1980); M. Bukowska-Strzyzewska and A. Tosik, *Acta Crystallogr., Sect. B* **B38**, 265, 950 (1982).

B. THEORETICAL AND QUANTUM CHEMICAL CALCULATIONS

There has been considerable interest in theoretical and quantum chemical calculations applied to the bipyridines over the past 25 years. π -Electron distributions, electron densities, and molecular orbital calculations on all the bipyridines have been determined, and the results are generally in accord with the known chemical reactions of the molecules.^{109,124-129} Calculations applied to 2,2', 3,3', and 4,4'-bipyridines have been correlated with ionization potentials,^{125,130} and reduction potentials^{109,131-134} and electrical susceptibilities of most of the bipyridines have been determined.¹³⁵ The ability of 3,3'- and 4,4'-bipyridines to act as electron-transfer bridges has been calculated.¹³⁶

There has been much interest in the predominant conformation of the bipyridines. Theoretical studies of the molecular structure of 2,2'-bipyridine suggest that the conformation with the nitrogen atoms transoid to one another is more stable than the cisoid form.^{125,137,138} In 3,3'-bipyridine, however, the cisoid form has nearly equal stability with the transoid conformation, and so the molecule is predicted to be a nearly free rotor through a large angle interval, whereas in 4,4'-bipyridine the minimum energy curve corresponds to a molecule with a large angle of twist.¹²⁵ Calculations based on photoelectron spectra are consistent with a near planar structure for 2,2'-bipyridine and suggest a nonplanar structure with a dihedral angle of about 45° for 4,4'-bipyridine.^{139,140} This angle is close to the value of 37.2° estimated for the interplanar angle in 4,4'-bipyridine from electron diffraction

¹²⁴ O. S. Otroschenko, V. B. Leont'ev, A. S. Sadykov, Y. S. Mangutova, and A. A. Korneichuk, *Zh. Obshch. Khim.* **34**, 2304 (1964).

¹²⁵ V. Galasso, G. De Alti and A. Bigotto, *Tetrahedron* **27**, 991 (1971).

¹²⁶ Y. S. Mangutova, V. B. Leont'ev, L. S. Mal'tseva, O. S. Otroschenko, and A. S. Sadykov, *Dokl. Akad. Nauk Uzb. SSR* **29**, 34 (1972) [*CA* **77**, 113623 (1972)].

¹²⁷ S. P. Sinha, *Rev. Roum. Chim.* **18**, 777 (1973).

¹²⁸ J. Reinhold, R. Benedix, P. Birner, and H. Hennig, *Z. Chem.* **17**, 115 (1977).

¹²⁹ A. T. Pilipenko, L. I. Savranskii, and V. A. Nikitina, *Dokl. Akad. Nauk SSSR* **246**, 625 (1979).

¹³⁰ R. L. Flurry, E. W. Stout, and J. J. Bell, *Theor. Chim. Acta* **8**, 203 (1967).

¹³¹ B. J. Tabner and J. R. Yandle, *J. Chem. Soc. A*, 381 (1968).

¹³² K. B. Wiberg and T. P. Lewis, *J. Am. Chem. Soc.* **92**, 7154 (1970).

¹³³ R. Held, F. Dietz, and P. Thomas, *Z. Chem.* **12**, 346 (1972).

¹³⁴ O. Guertler, K. P. Dietz, and P. Thomas, *Z. Anorg. Allg. Chem.* **396**, 217 (1973).

¹³⁵ E. F. McIntyre and H. F. Hameka, *J. Chem. Phys.* **70**, 2215 (1979).

¹³⁶ S. Larsson, *J. Am. Chem. Soc.* **103**, 4034 (1981).

¹³⁷ P. F. Franchini and G. Sbrana, *Trans. Faraday Soc.* **66**, 572 (1970).

¹³⁸ M. Bossa, G. Ramunni, and P. F. Franchini, *Theor. Chim. Acta* **17**, 327 (1970).

¹³⁹ J. P. Maier and D. W. Turner, *Faraday Discuss. Chem. Soc.* **54**, 149 (1972).

¹⁴⁰ I. Novak and L. Klasinc, *Z. Naturforsch. A* **33A**, 247 (1978).

studies in the gaseous state.¹⁴¹ Further calculations on the conformations of the bipyridines have been reported¹⁴²⁻¹⁴⁴ including molecular orbital studies of barriers to rotation in 2,2'-bipyridine.¹⁴⁵

Theoretical treatment of the spectra of the bipyridines has provided correlations between proton magnetic resonance spectra (PMR),¹⁴⁶⁻¹⁴⁸ ¹³C-NMR spectra,¹⁴⁹ ¹⁴N nuclear quadrupole resonances,¹⁵⁰ photoelectron spectra,¹⁵¹ two-photon absorption spectra,¹⁵² and electronic spectra,^{130,153-159} and various quantum chemical data. From the electronic-spectra calculations much evidence has been accumulated to support the transoid planar conformation for 2,2'-bipyridine in inert solvents. The electronic spectrum of the 4,4'-bipyridinium radical cation obtained by the one-electron reduction of **22**, sometimes known as dipyridyl violet, has also been the subject of theoretical calculations.¹⁶⁰

The triplet state of some of the bipyridines has interested several groups, sometimes in conjunction with electron paramagnetic resonance (EPR)

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transitions.^{151,161-166} From some of this work it is concluded that 2,2'-bipyridine exists in both cisoid and transoid conformations in the lowest triplet state.¹⁶⁷⁻¹⁷⁰ Electron spin densities and other calculations involving EPR spectra of the radical anions of 2,2'-¹⁷¹⁻¹⁷⁷ and 4,4'-bipyridine^{173,174,176,178-182} and 4,4'-bipyridinium radical cations¹⁷⁶ have been described. The nitrogen *1s* binding energies in a salt of 2,2'-bipyridine have been studied, using X-ray photoelectron spectroscopy.¹⁸³

C. DIPOLE MOMENTS

The dipole moment of 2,2'-bipyridine in benzene or carbon tetrachloride has been reported as less than 0.68,^{184,185} 0.91,¹⁵³ 0.69,⁸⁶ and 0.61 D.^{186,187} Because the conformation with the two nitrogen atoms transoid to each other should have a zero dipole moment and the cisoid configuration a value of 3.8 D, the consensus is that the molecule is in the transoid conformation and is approximately planar in solution with an angle of about 20° between

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the plane of the pyridine rings. Apparently resonance energies and dipole-dipole interactions are insufficient to hold the molecule in the strictly planar transoid form in solution, and rotation through an appreciable angle readily occurs. Calculations of the molar Kerr constants and the related Cotton-Mouton constants are in accord with this interpretation.^{186,188} Further studies of the dipole moment of 2,2'-bipyridine have been reported.^{143,189}

2,4'-Bipyridine and 3,4'-bipyridine have dipole moments of 3.84 and 2.38 D, respectively,⁸⁶ whereas 3,3'-bipyridine is calculated to have a value of 4.22 D in the cisoid form and 2.76 D in the transoid form.¹²⁵ 4,4'-Bipyridine has been found to have a dipole moment of less than 0.55^{184,185} and 0.31 D.⁸⁶ Because the planar molecule should have a zero dipole, it seems that 4,4'-bipyridine has a small angle ($\sim 10^\circ$) of twist between the planes of the pyridine rings in solution.^{86,184,185,190}

D. SPECTRA

1. Infrared and Raman Spectra

The infrared (IR) spectrum of 2,2'-bipyridine has been studied on numerous occasions both in the solid state and in solution within the range 40–4000 cm^{-1} .^{191–203} Detailed assignments of the spectra have been made including comparisons with the spectrum of biphenyl.^{191,192,194,196,197,200–202} The assignments are in agreement with theoretical calculations.²⁰⁴ The effects of high pressure on the IR spectrum of 2,2'-bipyridine in the range

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400–1500 cm^{-1} have been reported.²⁰⁵ The IR spectra of several ring-substituted 2,2'-bipyridines^{194,197} and 2,2':6',2''-terpyridine¹⁹⁸ have also been studied in detail. There has been considerable interest in the IR spectra of salts of 2,2'-bipyridine particularly from the viewpoint of the NH vibrations associated with possible intramolecular hydrogen bonding as in structure **23** and with interaction between the NH proton and the salt anion,^{193,206–209}

The IR spectra of 2,3'-bipyridine,^{196,200,210} 2,4'-bipyridine,²⁰⁰ 3,3'-bipyridine,^{191,196,200} and 3,4'-bipyridine^{200,211} have all been reported. From IR spectral assignments it is suggested that 2,3'- and 3,3'-bipyridines adopt the cisoid conformation.²⁰⁰ The IR spectrum of 4,4'-bipyridine both in the solid state and in solution has attracted much attention, and the spectrum has been fully interpreted.^{191,192,196,200,212} 4,4'-Bipyridine has been included in a study of the use of IR intensities as a quantitative measure of intramolecular interactions.²¹³ Interestingly, changes in the intensities of IR bands due to aromatic ring deformations and C—H deformations on going from the solid to the molten state have been used to show that the aromatic rings of 2,2'- and 4,4'-bipyridines are not coplanar in the liquid phase.^{214,215} The IR spectra of salts of 4,4'-bipyridine have been discussed.²¹⁶

The Raman spectra of 2,2'-bipyridine^{217–220} and 4,4'-bipyridine^{212,218} have been studied. The experimental data agree with theoretical calculations. The resonance Raman spectrum of the radical anion of 2,2'-bipyridine has also been investigated.²²¹ The Raman and IR spectra of 2,2'-bipyridine, using polarized light, have been obtained and assignments have been made.²²²

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2. Fluorescence and Phosphorescence Spectra

There is some difference of opinion about the ability of 2,2'-bipyridine to fluoresce. 2,2'-Bipyridine is weakly fluorescent in the solid state²²³ but has been reported not to fluoresce in a variety of organic solvents,^{224,225} although weak emissions have been obtained in cyclohexane and ethanol.²²⁶ In water, however, 2,2'-bipyridine has been reported²²⁶ to give a strong emission that has been attributed to the formation of a covalent hydrate.^{224,225} The monoprotonated bipyridinium cation also is claimed to fluoresce both on its own and as a covalent hydrate, whereas the bipyridinium dication exhibits no fluorescence. Contrary to this view, another group have found no fluorescence at room temperature in water with 2,2'-bipyridine and weak fluorescence with its monocation but describe a broad, structureless fluorescence band with the dication.²²⁷ The strong fluorescence previously observed in water with 2,2'-bipyridine and its monocation is attributed to the strong fluorescent properties of a zinc complex of 2,2'-bipyridine because of contamination of the water with zinc ions.²²⁸ Other studies of the fluorescence of 2,2'-bipyridine have been reported.²²⁹ The sterically hindered 3,3'-dimethyl-2,2'-bipyridine²²⁷ and 2,2':6',2''-terpyridine, however, give good fluorescence spectra, the latter in its monocationic form, giving an especially intense violet fluorescence.^{230,231} 4,4'-Bipyridine does not fluoresce.²²⁸ The cathodoluminescence of crystalline 2,2'-bipyridine and 4,4'-bipyridine has, however, received some attention.²³²

The phosphorescence spectra of 2,2'-bipyridine^{161,226,228,233-238} the sterically hindered 3,3'-dimethyl-2,2'-bipyridine,²²⁷ 4,4'-bipyridine,^{161,227,233,236,238} and the monoprotonated 4,4'-bipyridinium cation¹⁶⁶

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have been studied under a variety of conditions, and the lifetime of the phosphorescence has been discussed.^{233,234,239,240}

3. Ultraviolet Absorption Spectra

The UV absorption spectra of 2,2'-bipyridine,^{86,98,99,102,153,224,225,241–255} 2,3'-bipyridine,^{102,158,256} 2,4'-bipyridine,^{86,102,254} 3,3'-bipyridine,^{102,242,251} 3,4'-bipyridine,¹⁰² and 4,4'-bipyridine^{86,102,242,245,251,254} have been measured by several groups in different solvents. The spectra contain two regions of absorptions at about λ 240 and λ 275 nm. The spectra of 2,2':6',2''-terpyridines have also been studied.^{248,257,258} Studies of the absorption spectra of the bipyridines, especially 2,2'-bipyridine, at various pH values in aqueous solution have been reported.^{98,99,102,107,225,248–250,253} From this work it has been confirmed that 2,2'-bipyridine exists as the transoid conformation **1** in solution, whereas the monocation **21** favors a slightly twisted cisoid conformation. There is no evidence from UV spectral studies to support the intramolecular hydrogen-bonded structure **23** for the monocation of 2,2'-bipyridine.^{98,248,249} The dication **24** is believed to be in a slightly twisted transoid conformation. Likewise 2,2':6',2''-terpyridine (**25**) exists as the transoid-transoid conformation in solution.²⁴⁸ The polarized UV spectrum of 2,2'-bipyridine has been taken in oriented polyethylene films,²⁵² and the low-temperature (4.2 K) electronic spectra of 2,2'-bipyridine

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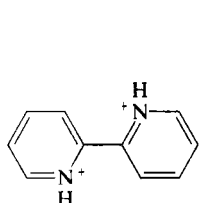
²⁵⁵ C. C. Deb, D. K. Hazra, and S. C. Lahiri, *Indian J. Chem., Sect. A* **21A**, 26 (1982).

²⁵⁶ T. C. Tso and R. N. Jeffrey, *Arch. Biochem. Biophys.* **43**, 269 (1953).

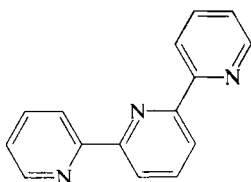
²⁵⁷ D. H. Wilkins and G. F. Smith, *Anal. Chim. Acta* **9**, 338 (1953).

²⁵⁸ J. M. Rao, D. J. Macero, and M. C. Hughes, *Inorg. Chim. Acta* **41**, 221 (1980).

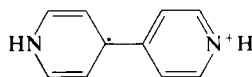
and 4,4'-bipyridine in single mixed crystals with biphenyl have been interpreted.²⁵⁹



(24)



(25)



(26)

4. Nuclear Magnetic Resonance Spectra

The proton NMR spectrum of 2,2'-bipyridine has been obtained and analyzed in a variety of solvents by several authors.^{251,260-270} The full interpretation of the spectra is in accord with the transoid conformation **1** in solution. The behavior of the chemical shifts of protons at positions 3 and 3' indicates the existence of a strong deshielding effect exerted by the nitrogen atoms of the adjacent rings.^{251,264,265} Interestingly, the proton NMR spectra of 2,2'-bipyridine taken in various solvents indicate self-association and stacking of the molecules in some cases.²⁷¹ The spectra of some substituted 2,2'-bipyridines,^{251,272,273} 2,3'-bipyridine,²⁷⁰ 2,4'-bipyridine,²⁷⁰ 3,3'-bipyridine,²⁵¹ and 4,4'-bipyridine^{109,251,270} have been investigated in detail. It was

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²⁶⁹ B. Jezowska-Trzebiatowska, H. Kozłowski, L. Latos-Grazynski, and T. Kowalik, *Chem. Phys. Lett.* **30**, 355 (1975).

²⁷⁰ A. J. de Koning, P. H. M. Budzelaar, J. Boersma, and G. J. M. Van der Kerk, *J. Organomet. Chem.* **199**, 153 (1980).

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²⁷² F. A. Hart, J. E. Newbery, and D. Shaw, *J. C. S. Chem. Commun.*, 45 (1967).

²⁷³ T. L. J. Huang and D. G. Brewer, *Can. J. Chem.* **59**, 1689 (1981).

concluded that 3,3'-bipyridine and 4,4'-bipyridine are probably highly twisted in all solvents or else behave as essentially free rotors.²⁵¹ The spectrum of 2,2':6',2''-terpyridine confirms that the compound prefers the transoid-transoid conformation in solution.^{268,274} The proton NMR spectra of 2,2'-, 2,3'-, 3,3'-, and 4,4'-bipyridines and several of their substituted derivatives have also been used to calculate barriers to internal rotation.^{147,148} ¹³C chemical shifts of 2,2'-bipyridine,^{149,270,275-278} some substituted 2,2'-bipyridines,²⁷⁸ 2,3'-bipyridine,^{149,270,279} 2,4'-bipyridine,²⁷⁰ 3,3'-bipyridine,¹⁴⁹ 4,4'-bipyridine,^{149,270} and 2,2':6',2''-terpyridine,¹⁴⁹ ¹⁴N chemical shifts of some bipyridines,^{280,281} and ¹⁵N chemical shifts of 2,2'-bipyridine²⁸² have been measured. The proton NMR spectrum of 4,4'-bipyridine in a nematic phase solution led to the conclusion that there was rapid rotation about the interring C—C bond²⁸³ with positions having an interring angle of about 30° being the most populated. There are also some deviations from the planar transoid form with 2,2'-bipyridine in a nematic phase solution.²⁸⁴

5. Mass Spectra

The electron-impact mass spectra of 2,2'-bipyridine²⁸⁵⁻²⁸⁸ and 4,4'-bipyridine^{285,288,289} have been examined. As expected, the spectra are dominated by the molecular ions that fragment by loss of H⁺, CN⁺, C₂H₂, and

²⁷⁴ H. Elsbernd and J. K. Beattie, *J. Inorg. Nucl. Chem.* **34**, 771 (1972).

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²⁸⁹ N. G. Keats and L. A. Summers, *J. Heterocycl. Chem.* **13**, 753 (1976).

HCN.^{287,289} The spectra of 2,3'-bipyridine,²⁰ 2,2':6',2''-terpyridine,²⁸⁸ nemertelline (**11**),²⁰ some substituted 2,3'-bipyridines,²⁹⁰ and 4,4'-bipyridines²⁹¹ have been briefly discussed, and the fragmentation patterns of hydroxy- and alkoxy-2,2'-bipyridines,^{292,293} 2,2'-bipyridine-5-carboxylic acid, 2,2'-bipyridine-5-sulfonic acid,²⁹⁴ and 6-halogeno-2,2'-bipyridines²⁹⁵ have been covered in detail. The doubly charged ion mass spectrum of 2,2'-bipyridine has recently been reported.²⁹⁶

6. Electron Paramagnetic Resonance Spectra

The electron spin resonance (ESR) spectra of the radical anion of 2,2'-bipyridine,^{171,173,297,298} sometimes in the form of its alkali metal complex,^{171,175,177,299-304} the radical anion of 3,3'-bipyridine,³⁰⁵ and the radical anion of 4,4'-bipyridine,^{173,179,306-312} usually obtained by reduction of the bipyridines with an alkali metal, have been measured, and hyperfine splitting constants were assigned. Related biradical species have also been investigated.³¹³ The ESR spectrum of the 4,4'-bipyridinium radical cation, of which

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²⁹⁵ N. G. Keats and L. A. Summers, *J. Heterocycl. Chem.* **16**, 1431 (1979).

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³¹⁰ T. Iizuka and K. Tanabe, *Bull. Chem. Soc. Jpn.* **48**, 2527 (1975).

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³¹³ J. D. W. Van Voorst, W. G. Zijlstra, and R. Sitters, *Chem. Phys. Lett.* **1**, 321 (1967).

26 is one canonical form, has been investigated and interpreted.^{314–319} The radical cation **26** is obtained by reduction of 4,4'-bipyridine dihydrohalides.

7. Miscellaneous Spectra

The ¹⁴N nuclear quadrupole resonance absorption spectra of 2,2'-bipyridine and 4,4'-bipyridine have been measured,¹⁵⁰ and the photoelectron spectra of the same bipyridines and 2,2':6',2''-terpyridine have been investigated.^{139,140} Two-photon absorption spectra³²⁰ of 2,2'-bipyridine have been taken.^{321–323}

E. IONIZATION PROPERTIES

The bipyridines are dibasic, and the two acid dissociation constants K_1 and K_2 , for all the bipyridines have been determined. Typical values are recorded in Table I. There has been considerable interest in the first dissociation constants K_1 of 2,2'-bipyridine and substituted 2,2'-bipyridines because of their use as metal complexing agents.³²⁴ In general, the order of relative basic strengths of derivatives of 2,2'-bipyridine is as expected. Electron-attracting substituents reduce the basicity, whereas electron-donating substituents increase the basicity of the molecule.^{104,197,250,325–328} The dissociation constants of several substituted bipyridines correlate well with the Hammett equation.¹⁹⁷ 2,2'-Bipyridines with an electron-donating substituent at position 4 are monoprotonated at N-1 and not at N-1'.³²⁶

³¹⁴ J. R. Bolton, A. Carrington, and J. dos Santos-Veiga, *Mol. Phys.* **5**, 465 (1962).

³¹⁵ F. Bruin, F. W. Heineken, M. Bruin, and A. Zahlan, *J. Chem. Phys.* **36**, 2783 (1962).

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³²⁴ W. A. E. McBryde, "A Critical Review of Equilibrium Data for Proton and Metal Complexes of 1,10-Phenanthroline, 2,2'-Bipyridyl and Related Compounds," I.U.P.A.C. Chem. Data Ser., No. 17. Pergamon, Oxford, 1978.

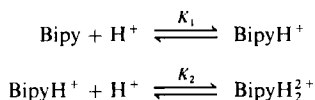
³²⁵ M. Yasuda, K. Sone, and K. Yamasaki, *J. Phys. Chem.* **60**, 1667 (1956).

³²⁶ M. J. Cook, A. R. Katritzky, and S. Nadji, *J. C. S. Perkin II*, 1215 (1978).

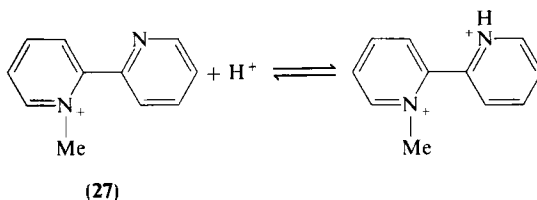
³²⁷ M. A. Weiner and A. Basu, *Inorg. Chem.* **19**, 2797 (1980).

³²⁸ D. Sengupta and S. C. Lahiri, *Indian J. Chem., Sect. A* **21A**, 31 (1982).

Thermodynamic data for the ionization equilibria of 2,2'-bipyridine have also been obtained^{99,100,103,329-332} as well as kinetic data.³³³



The most striking result in the list of dissociation constants in Table I is the very low $\text{p}K_2$ value for 2,2'-bipyridine compared with its isomers. 2,2'-Bipyridine was for some time considered to be only monobasic, unable to combine with a second proton in acid solution.^{100,102} Whereas this view is no longer tenable, the reasons for the low $\text{p}K_2$ value of 2,2'-bipyridine have been the subject of some debate. Some authors consider the breaking of an intramolecular hydrogen bond in the monocation **23**, which exists in a slightly twisted cisoid conformation to be a factor,¹⁰⁶ although others dispute that it is of much importance.¹⁰⁷ Clearly, however, the two nitrogen atoms in the dication, which adopts a slightly twisted transoid conformation (**24**), are still close together with large electrostatic effects in operation. This proximity is largely responsible for the low $\text{p}K_2$ of 2,2'-bipyridine. Interestingly, the $\text{p}K$ value for the protonation of the 1-methyl-2,2'-bipyridinium ion (**27**) is also low (+0.31).¹⁰⁷



The ionization constants of 2,2'-bipyridine in various organic solvent and water mixtures,^{100,102,334-338} at different ionic strengths³³⁹⁻³⁴² and at

³²⁹ P. Krumholz, *J. Am. Chem. Soc.* **71**, 3654 (1949).

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³⁴² A. Bhattacharyya and S. C. Lahiri, *J. Indian Chem. Soc.* **58**, 706 (1981).

various temperatures, have been studied.³³¹ Thermodynamic data for the mixed solvent systems have been determined.³⁴³⁻³⁴⁶ Experiments in the highly polar solvent oxypropionitrile have also been reported.³⁴⁷ The dissociation constants of 2,2':6,2''-terpyridine^{104,330,348-350} and of 2,2'-bipyridine and 4,4'-bipyridine in the excited state have been discussed.^{227,327,351}

F. CHROMATOGRAPHY

Experimental and theoretical studies of the behavior of 2,2', 2,3', 3,3', and 4,4'-bipyridines in paper^{16,256,352} and thin-layer chromatography³⁵³⁻³⁶³ and of 2,2'- and 4,4'-bipyridines in linear-elution adsorption,^{364,365} gas,³⁶⁶⁻³⁶⁸ and gas-liquid chromatography³⁶⁹ have been de-

³⁴³ A. K. Ray, *J. Chem. Eng. Data* **22**, 2 (1977).

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³⁵² M. Przyborowska, *Chem. Anal. (Warsaw)* **20**, 1191 (1975).

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³⁶⁵ S. Gigi, V. Paucescu, D. M. Rizescu, and I. Neacsu, Romanian Patent 58,782 (1975) [CA **88**, 152444 (1978)].

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³⁶⁸ R. D. Schwartz and R. G. Mathews, *J. Chromatogr.* **126**, 113 (1976).

³⁶⁹ J. D. Ramsey, T. D. Lee, M. D. Osselson, and A. C. Moffat, *J. Chromatogr.* **184**, 185 (1980).

scribed. A gas chromatographic method of analysis of 2,3'-bipyridine, using 2,4'-bipyridine as internal standard, has been developed.³⁷⁰ Work on the adsorption of 2,2'-bipyridine on silica gels³⁷¹ and studies on paper¹⁶ and thin-layer chromatography³⁵⁶ of some terpyridines have also been reported.

G. MISCELLANEOUS PROPERTIES

The polarographic behavior of all the bipyridines with the exception of the 3,4'-isomer has been investigated in aqueous solution. The difficulty of reduction increases in the order 4,4'-, 2,4'-, 2,3'-, 2,2'-, and 3,3'-bipyridine.³⁷² Most of the work has been concerned with 2,2'- and 4,4'-bipyridines. Both isomers are reduced in aqueous solution by a two-electron process, sometimes observed as two separate one-electron steps, which is pH dependent because of the formation of a dihydro derivative.³⁷²⁻³⁷⁹ Complications in interpretation of the waves due to prewaves, catalytic hydrogen waves, wave maxima, and adsorption phenomena have frequently been observed.^{372,375-377,380-387} Polarography and cyclic voltammetry investigations have been extended to the study of 2,2'- and 4,4'-bipyridines

³⁷⁰ R. F. Severson, K. L. McDuffie, R. F. Arrendale, G. R. Gwynn, J. F. Chaplin, and A. W. Johnson, *J. Chromatogr.* **211**, 111 (1981).

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³⁸⁰ M. T. Falqui and M. Secci, *Rend. Semin. Fac. Sci. Univ. Cagliari* **26**, 190 (1956) [*CA* **52**, 12621 (1958)].

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³⁸³ J. Volke, *Abhl. Dtsch. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.*, 70 (1964) [*CA* **63**, 2631 (1965)].

³⁸⁴ H. Sawamoto, *Bull. Chem. Soc. Jpn.* **43**, 2096 (1970).

³⁸⁵ E. A. Mambetkaziev, S. I. Zhdanov, B. B. Damaskin, V. N. Statsyuk, A. Shaldybaeva, and B. Tuletaev, *Nov. Polyarogr., Tezisy Dokl. Vses. Soveshch. Polyarogr.*, 6th, 1975, 117 (1975) [*CA* **86**, 23503 (1977)].

³⁸⁶ H. Sawamoto, *Nippon Kagaku Kaishi*, 679 (1977).

³⁸⁷ N. K. Akhmetov, R. I. Kaganovich, B. B. Damaskin, and E. A. Mambetkaziev, *Elektrokhimiya* **14**, 1761 (1978).

in nonaqueous solvents.^{131,132,134,203,327} Perfluoro-3,3'-bipyridine and perfluoro-4,4'-bipyridine have also been studied by voltammetry.³⁸⁸ The polarography of the diprotonated, 4,4'-bipyridinium dication, which is present in strong acid solution, has been studied. It is reduced to a radical cation **26** at a potential (E_0) of -0.485 V.³⁸⁹

The ionization potentials of some of the bipyridines have been investigated.³⁹⁰ Solubility data for 2,2'-bipyridine in aqueous solution,³⁹¹ in aqueous solvent mixtures,^{345,392} and in various aqueous salt solutions have been obtained,³⁹³ whereas the heat of solution, heat capacities, and related data for 2,2'- and 4,4'-bipyridines in water have been measured.^{394,395} The enthalpies of solution of 2,2'-bipyridine in water and aqueous solvent mixtures have also been obtained.³⁹⁶ Dielectric relaxation studies of 2,2'-bipyridine in carbon tetrachloride have been reported in connection with hindered internal rotation.³⁹⁷ Partition coefficients for 2,2'-bipyridine between water and various organic solvents have been measured.³⁹⁸

III. Syntheses

A. 2,2'-BIPYRIDINE

2,2'-Bipyridine was first prepared in 1888 by the dry distillation of the copper salt of picolinic acid.³⁹⁹ This method and modifications give low yields of 2,2'-bipyridine.^{84,400-402} Another old method involves oxidation of 1,10-phenanthroline (**28**) to 2,2'-bipyridine-3,3'-dicarboxylic acid (**29**) by alkaline permanganate, followed by decarboxylation.^{96,399,403,404} This

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³⁹⁵ O. Enea, C. Jolicoeur, and L. G. Hepler, *Can. J. Chem.* **58**, 704 (1980).

³⁹⁶ J. Burgess and R. Sherry, *J. C. S. Perkin II*, 366 (1981).

³⁹⁷ D. D. Klug, D. E. Kranbuehl, and W. E. Vaughan, *J. Chem. Phys.* **53**, 4187 (1970).

³⁹⁸ H. Irving and D. H. Mellor, *J. Chem. Soc.*, 5222 (1962).

³⁹⁹ F. Blau, *Ber. Dtsch. Chem. Ges.* **21**, 1077 (1888).

⁴⁰⁰ G. Cavicchi, *Ann. Chim. (Rome)* **40**, 153 (1950).

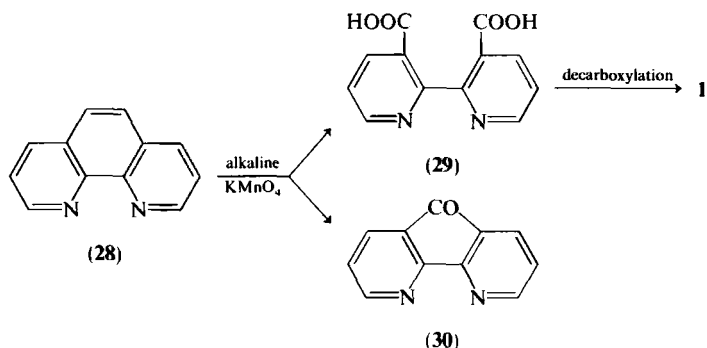
⁴⁰¹ D. Oda, *Nippon Kagaku Zasshi* **75**, 987 (1954).

⁴⁰² F. Kuffner and C. Russo, *Monatsh. Chem.* **85**, 1097 (1954).

⁴⁰³ G. E. Inglett and G. F. Smith, *J. Am. Chem. Soc.* **72**, 842 (1950).

⁴⁰⁴ D. Aziz and J. G. Breckenridge, *Can. J. Res., Sect. B* **28**, 26 (1950).

method has been adopted to prepare ^{14}C -labeled 2,2'-bipyridine.⁴⁰⁵ It has subsequently been found that the diazafluorenone **30** is consistently a coproduct of the oxidation of **28** along with **29**.⁴⁰⁶ The mechanism of



the oxidation, which involves among others, the formation of 1,10-phenanthroline-5,6-dione as intermediate, has been studied.²⁸⁶ 5-Methyl-2,2'-bipyridine has been obtained in this way from 3-methyl-1,10-phenanthroline.⁴⁰⁷ The Ullmann reaction has also been used to prepare 2,2'-bipyridine by treating a 2-halopyridine, preferably 2-bromopyridine, with copper powder in a high-boiling solvent.^{87,408-414} Raney nickel may be used instead of copper.⁴¹⁵ The Ullmann reaction has been adapted for the preparation of symmetrically substituted 2,2'-bipyridines,⁴¹⁶⁻⁴²² 2,2':6',2''-terpyridine, and

⁴⁰⁵ P. Ellis, R. G. Wilkins, and M. J. G. Williams, *J. Chem. Soc.*, 3975 (1956).

⁴⁰⁶ I. F. Eckhard and L. A. Summers, *Aust. J. Chem.* **26**, 2727 (1973).

⁴⁰⁷ K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.* **85**, 2532 (1963).

⁴⁰⁸ F. H. Burstall, *J. Chem. Soc.*, 1662 (1938).

⁴⁰⁹ T. A. Geissman, M. J. Schlatter, I. D. Webb, and J. D. Roberts, *J. Org. Chem.* **11**, 741 (1946).

⁴¹⁰ G. I. Mikhailov, *Zh. Prikl. Khim.* **28**, 114 (1955).

⁴¹¹ Z. Kulicki and W. Karminski, *Zesz. Nauk. Politech. Slask., Chem.* **16**, 11 (1963) [*CA* **62**, 4001 (1965)].

⁴¹² W. Karminski and Z. Kulicki, *Chem. Stosow., Ser. A* **9**, 129 (1965) [*CA* **63**, 18018 (1965)].

⁴¹³ Z. Kulicki, W. Karminski, and B. Kajzerek, Polish Patent 52,038 (1966) [*CA* **68**, 2816 (1968)].

⁴¹⁴ M. Goshayev, O. S. Otroschenko, A. S. Sadykov, and N. Kuznetsova, *Izv. Akad. Nauk. Turkm. SSR, Ser. Fiz.-Tekh., Khim. Geol. Nauk.*, 114 (1970) [*CA* **74**, 3480 (1971)].

⁴¹⁵ G. H. Lang, German Patent 2,521,969 (1975) [*CA* **84**, 105407 (1976)].

⁴¹⁶ F. H. Case, *J. Am. Chem. Soc.* **68**, 2574 (1946).

⁴¹⁷ F. H. Case and T. J. Kasper, *J. Am. Chem. Soc.* **78**, 5842 (1956).

⁴¹⁸ J. J. Porter and J. L. Murray, *J. Am. Chem. Soc.* **87**, 1628 (1965).

⁴¹⁹ T. Kametani, K. Ogasawara, A. Kozuka, and M. Shio, *Yakugaku Zasshi* **87**, 254 (1967).

⁴²⁰ T. Kauffmann, E. Wienhofer, and A. Woltermann, *Angew. Chem., Int. Ed. Engl.* **10**, 741 (1971).

⁴²¹ L. Kaczmarek and P. Nantka-Namirski, *Acta Pol. Pharm.* **36**, 629 (1979).

⁴²² J. A. H. MacBride, P. M. Wright, and B. J. Wakefield, *Tetrahedron Lett.*, 4545 (1981).

polypyridines.⁴⁰⁸ With some highly substituted bromopyridines the coupling reaction proceeds very easily.⁴²³ In a related process, 2-chloropyridine is converted to 2,2'-bipyridine in 50% yield by reaction with alkaline sodium formate in the presence of palladium on charcoal and a surfactant.⁴²⁴ Grignard reagents derived from 2-bromopyridine also decompose in the presence of heavy metal halides to afford 2,2'-bipyridine.^{415,425}

The most satisfactory and economical methods for the preparation of 2,2'-bipyridine use pyridine as starting material. Several methods have been used to convert pyridine to 2,2'-bipyridine, a reaction that is essentially an oxidation or dehydrogenation. Simple thermal dehydrogenation or pyrolysis of pyridine at high temperatures produces some 2,2'-bipyridine along with other isomeric bipyridines, terpyridines, and numerous by-products.⁴²⁶⁻⁴²⁹ This method has also been used to prepare symmetrically substituted 2,2'-bipyridines.⁴²⁶ The incorporation of an oxidizing or dehydrogenating agent assists the process, enabling the reaction to proceed at lower temperatures ($\sim 250\text{--}350^\circ\text{C}$).^{85,88,430-438} Dimethyl-2,2'-bipyridines are likewise made from picolines,^{416,439} and similar couplings to give substituted 2,2'-bipyridines have been reported with 1-methylanabasine⁴⁴⁰ and certain 3-pyridinols.⁴⁴¹ The oxidation of pyridine by potassium peroxydisulfate in aqueous alkaline solution also affords some 2,2'-bipyridine (20% yield) along with 2,2':6',2''-terpyridine,⁴⁴²⁻⁴⁴⁴ and persulfate oxidation gives sim-

⁴²³ H. J. den Hertog and B. Mulder, *Recl. Trav. Chim., Pays-Bas* **68**, 433 (1949).

⁴²⁴ P. Bamfield and P. M. Quan, *Synthesis*, 537 (1978).

⁴²⁵ Y. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and M. Goshaev, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 85 (1969) [*CA* **73**, 98760 (1970)].

⁴²⁶ H. Meyer and A. Hofmann-Meyer, *J. Prakt. Chem.* **102**, 287 (1921).

⁴²⁷ P. Krumholz, "*Sel. Chim.*" **8**, 3 (1949) [*CA* **44**, 3992 (1950)].

⁴²⁸ R. H. Linnell, *Toh. Sci.* **6**, 104 (1962).

⁴²⁹ J. R. Case, British Patent 995,689 (1965) [*CA* **63**, 9923 (1965)].

⁴³⁰ F. Hein and W. Retter, *Ber. Dtsch. Chem. Ges. B* **61**, 1790 (1928).

⁴³¹ A. H. Jubb, British Patent 869,954 (1961) [*CA* **56**, 3465 (1962)].

⁴³² P. F. H. Freeman and R. Ghosh, U.S. Patent 2,962,502 (1960) [*CA* **55**, 8440 (1961)].

⁴³³ A. H. Jubb, British Patent 869,955 (1961) [*CA* **56**, 461 (1962)].

⁴³⁴ G. H. Lang, British Patent 1,014,076 (1965) [*CA* **64**, 9691 (1966)].

⁴³⁵ A. J. Osborn, British Patent 1,060,661 (1967) [*CA* **67**, 21823 (1967)].

⁴³⁶ H. D. T. Willink and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas* **50**, 287 (1931).

⁴³⁷ G. B. Bonino, F. Gesmundo, P. F. Rossi, and A. Passerone, *Chim. Ind. (Milan)* **50**, 1103 (1968).

⁴³⁸ S. A. Potter, German Patent 2,140,529 (1972) [*CA* **77**, 5347 (1972)].

⁴³⁹ H. D. T. Willink and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas* **54**, 275 (1935).

⁴⁴⁰ O. S. Otroshchenko, A. A. Ziyaev, A. S. Sadykov, and G. A. Tolkacheva, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 179 (1969) [*CA* **73**, 120459 (1970)].

⁴⁴¹ J. G. Wirth, U.S. Patent 3,767,652 (1973) [*CA* **80**, 109920 (1974)].

⁴⁴² P. Moeckel and G. Staerk, British Patent 870,700 (1961) [*CA* **56**, 3564 (1962)].

⁴⁴³ P. Moeckel and G. Staerk, German (East) Patent 23,118 (1962) [*CA* **58**, 3403 (1963)].

⁴⁴⁴ P. Moeckel and G. Staerk, *Z. Chem.* **7**, 21 (1967).

ilar results.⁴⁴⁵ Some 2,2'-bipyridine is produced along with several other products from the reaction of *tert*-butyl peroxide with pyridine.⁴⁴⁶

A considerable improvement in the preparation of 2,2'-bipyridine from pyridine was discovered in 1956 with the use of the metal catalyst Raney nickel for the conversion. Following from earlier work with nickel catalysts,⁴⁴⁷⁻⁴⁴⁹ Badger and Sasse⁴⁵⁰ discovered that 2,2'-bipyridine was formed by reaction of degassed Raney nickel with pyridine at its boiling point. No isomeric bipyridines were detected among the reaction products. The 2,2'-bipyridine was readily purified from small amounts of 2,2':6',2''- and 2,2':5',2''-terpyridines and an organonickel complex^{451,452} and from unchanged pyridine, which was removed by distillation. Modifications of this process have made it the preferred method for the synthesis of 2,2'-bipyridine.⁴⁵³⁻⁴⁵⁶ A review of the process has appeared.⁴⁵⁷ It has been developed as an industrial method for the manufacture of 2,2'-bipyridine⁴⁵⁸⁻⁴⁶⁶ on the scale necessary for the synthesis of the herbicide diquat (see Section IV,D).⁴⁶⁷ Other Raney catalysts, for example, Raney cobalt and Raney copper, are less effective.^{468,469} Symmetrically substituted

⁴⁴⁵ J. Russell and R. H. Thomson, *J. Chem. Soc.*, 3379 (1962).

⁴⁴⁶ K. Schwetlick and R. Lungwitz, *Z. Chem.* **4**, 458 (1968).

⁴⁴⁷ J. P. Wibaut and L. M. F. Van de Lande, *Recl. Trav. Chim. Pays-Bas* **48**, 1005 (1929).

⁴⁴⁸ J. P. Wibaut and H. D. T. Willink, *Recl. Trav. Chim. Pays-Bas* **50**, 287 (1931).

⁴⁴⁹ J. I. Jones, *J. Chem. Soc.*, 1392 (1950).

⁴⁵⁰ G. M. Badger and W. H. F. Sasse, *J. Chem. Soc.*, 616 (1956).

⁴⁵¹ A. M. Sargeson and W. H. F. Sasse, *Proc. Chem. Soc., London*, 150 (1958).

⁴⁵² W. H. F. Sasse and C. P. Whittle, *Aust. J. Chem.* **16**, 31 (1963).

⁴⁵³ W. H. F. Sasse, *J. Chem. Soc.*, 3046 (1959).

⁴⁵⁴ W. H. F. Sasse, *Org. Synth.* **46**, 5 (1966).

⁴⁵⁵ G. H. Lang, R. G. A. New, and J. M. Thompson, British Patent 960,176 (1964) [*CA* **62**, 7734 (1965)].

⁴⁵⁶ W. H. F. Sasse and C. P. Whittle, *Aust. J. Chem.* **16**, 14 (1963).

⁴⁵⁷ G. M. Badger and W. H. F. Sasse, *Adv. Heterocycl. Chem.* **2**, 179 (1963).

⁴⁵⁸ G. H. Lang, R. G. A. New, and J. M. Thompson, British Patent 899,015 (1962) [*CA* **57**, 6670 (1962)].

⁴⁵⁹ Imperial Chemical Industries of Australia and New Zealand, Ltd., British Patent 897,473 (1962) [*CA* **57**, 13739 (1962)].

⁴⁶⁰ G. L. Varcoe, U.S. Patent 3,053,846 (1962) [*CA* **58**, 6807 (1963)].

⁴⁶¹ G. L. Varcoe, Australian Patent 245,072 (1963) [*CA* **64**, 17552 (1966)].

⁴⁶² G. L. Varcoe, German Patent 1,445,079 (1969) [*CA* **72**, 21615 (1970)].

⁴⁶³ J. A. Joy and D. C. Marshall, German Patent 2,230,560 (1973) [*CA* **78**, 111132 (1973)].

⁴⁶⁴ D. C. Marshall, British Patent 1,202,711 (1970) [*CA* **73**, 102478 (1970)].

⁴⁶⁵ L. D. Gluzman, L. P. Stolyarenko, and S. N. Ol'shanskaya, *Sb. Nauchn. Tr., Ukr. Nauchno-Issled. Uglekhim. Inst.* **20**, 160 (1967) [*CA* **70**, 3770 (1969)].

⁴⁶⁶ M. Cieslak and M. Koperska, *Pr. Inst. Przem. Org.* **2**, 21 (1970) [*CA* **78**, 43213 (1973)].

⁴⁶⁷ L. A. Summers, "The Bipyridinium Herbicides," Academic Press, New York, 1980.

⁴⁶⁸ G. M. Badger, G. D. F. Jackson, and W. H. F. Sasse, *J. Chem. Soc.*, 4438 (1960).

⁴⁶⁹ G. D. F. Jackson, W. H. F. Sasse, and C. P. Whittle, *Aust. J. Chem.* **16**, 1126 (1963).

2,2'-bipyridines may be obtained by the Raney-nickel process from substituted pyridines.^{203,450,470-474} Other metal catalysts, for example, palladium on carbon, are not usually as effective or of use at such low temperatures as the degassed Raney-nickel process for the preparation of 2,2'-bipyridine from pyridine,^{469,475-483} but degassed palladium on carbon catalyst has been used to prepare 6,6'-dimethyl-2,2'-bipyridine from 2-picoline⁴⁸⁴ and 4,4'-dimethyl-2,2'-bipyridine from 4-picoline.⁴⁸⁵ Some symmetrically substituted 2,2'-bipyridines are obtained in better yield using rhodium on carbon catalyst rather than Raney nickel,⁴⁸⁶ and 2,2':6',2"-terpyridines are better prepared using palladium on carbon.^{487,488}

Pyridine 1-oxide either alone or as a mixture with pyridine has occasionally been used as starting material for the preparation of 2,2'-bipyridine, using palladium or platinum catalysts. Sometimes 2,2':6',2"-terpyridine is formed as well.⁴⁸⁹⁻⁴⁹¹ The method has been extended to the preparation of substituted 2,2'-bipyridines.⁴⁹¹⁻⁴⁹³ Piperidine hydrochloride can be used

⁴⁷⁰ W. H. F. Sasse and C. P. Whittle, *J. Chem. Soc.*, 1347 (1961).

⁴⁷¹ G. H. Lang, British Patent 955,951 (1964) [CA 61, 3075 (1964)].

⁴⁷² F. A. Hart and J. E. Newbery, *J. Inorg. Nucl. Chem.* 31, 1725 (1969).

⁴⁷³ O. S. Otroshchenko, A. A. Ziyaev, and A. S. Sadykov, U.S.S.R. Patent 255,276 (1969) [CA 72, 111307 (1970)].

⁴⁷⁴ A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, K. D. Khalilova, and G. A. Tolkacheva, *Khim. Geterotsikl. Soedin.*, 1224 (1978).

⁴⁷⁵ H. Rapoport, R. Iwamoto, and J. R. Tretter, *J. Org. Chem.* 25, 372 (1960).

⁴⁷⁶ California Research Corporation, British Patent 915,950 (1963) [CA 59, 11453 (1963)].

⁴⁷⁷ G. H. Lang, British Patent 981,353 (1965) [CA 63, 14826 (1965)].

⁴⁷⁸ G. H. Lang and R. G. A. New, British Patent 1,000,656 (1965) [CA 63, 16315 (1965)].

⁴⁷⁹ G. H. Lang, British Patent 1,026,822 (1966) [CA 65, 2232 (1966)].

⁴⁸⁰ R. F. Dalton, D. A. Dowden, and G. H. Lang, British Patent 1,377,213 (1974) [CA 82, 170703 (1975)].

⁴⁸¹ D. Y. Waddan and D. Williams, German Patent 1,950,074 (1970) [CA 73, 3799 (1970)].

⁴⁸² J. Haginiwa, Y. Higuchi, and I. Maki, *Yakugaku Zasshi* 97, 1261 (1977).

⁴⁸³ R. Vilceanu, I. Neda, E. Arsulescu, O. Leonte, and S. Kutz, Romanian Patent 67,302 (1979) [CA 94, 208723 (1981)].

⁴⁸⁴ R. H. Fabian, D. M. Klassen, and R. W. Sonntag, *Inorg. Chem.* 19, 1977 (1980).

⁴⁸⁵ P. K. Ghosh and T. G. Spiro, *J. Am. Chem. Soc.* 102, 5543 (1980).

⁴⁸⁶ J. C. Carey and W. H. F. Sasse, *Aust. J. Chem.* 21, 207 (1968).

⁴⁸⁷ P. E. Rosevear and W. H. F. Sasse, *J. Heterocycl. Chem.* 8, 483 (1971).

⁴⁸⁸ P. E. Rosevear and W. H. Sasse, Australian Patent 466,960 (1975) [CA 84, 74118 (1976)].

⁴⁸⁹ G. H. Lang, British Patent 1,014,077 (1965) [CA 64, 11182 (1966)].

⁴⁹⁰ J. Haginiwa and Y. Higuchi, *Yakugaku Zasshi* 93, 144 (1973).

⁴⁹¹ T. Haginiwa, Y. Higuchi, and Y. Fujimoto, Japanese Patent 13,796 (1974) [CA 81, 153148 (1974)].

⁴⁹² J. Haginiwa, Y. Higuchi, T. Kawashina, and T. Goto, *Yakugaku Zasshi* 95, 204 (1975).

⁴⁹³ J. Haginiwa, Y. Higuchi, Y. Hirawata, N. Hoshino, and H. Sakakura, *Yakugaku Zasshi* 99, 1176 (1979).

instead of pyridine⁴⁹⁴ in the process and 1-methylpyridinium salts instead of pyridine 1-oxide.⁴⁹⁵

An important method for the synthesis of bipyridines involves reaction of an alkali metal, such as sodium or magnesium, with pyridine. This process results in the formation of several isomeric bipyridines, including 2,2'-bipyridine, but the predominant isomer formed is usually 4,4'-bipyridine. This method is covered in the section devoted to the synthesis of 4,4'-bipyridine (Section III,F). 4-Substituted pyridines, however, readily give 4,4'-disubstituted 2,2'-bipyridines on reaction with sodium.^{496,497} If however, pyridine 1-oxide replaces pyridine in the reaction with sodium, a good yield (44%) of 2,2'-bipyridine, largely free of isomeric bipyridines, can be obtained. Deoxygenation of the 1-oxide accompanies the dimerization.⁴⁹⁸⁻⁵⁰⁰

A number of routes are available for the synthesis of 2,2'-bipyridines where one of the pyridine rings is built up from simpler entities. For example, condensation of 2-(aminomethyl)pyridine (**31**) with acetaldehyde or acetylene over a silicon-alumina catalyst at 450°C gives 2,2'-bipyridine,⁵⁰¹ whereas 2-cyanopyridine reacts with acetylene at 120°C in the presence of a cobalt catalyst to afford 2,2'-bipyridine in 95% yield.⁵⁰² 2-Acetylpyridine with acrolein and ammonia gives 2,2'-bipyridine in the presence of dehydrating and dehydrogenating catalysts,⁵⁰³ and related condensations afford substituted 2,2'-bipyridines.^{504,505} In a similar vein, condensation of benzaldehyde with 2 mol of 2-acetylpyridine in the presence of ammonia at 250°C affords 2,6-di(2-pyridyl)-4-phenylpyridine,⁵⁰⁶ and related syntheses of substituted 2,2':6',2''-terpyridines have been described.^{417,507,508} Likewise, formaldehyde with two moles of ethyl picolinoylacetate and ammonia, followed by oxidation of the product and hydrolysis and decarboxylation, affords a good

⁴⁹⁴ A. S. Kurbatova, Y. V. Kurbatov, A. Palamar, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 17 (1969) [*CA* **75**, 35645 (1971)].

⁴⁹⁵ R. F. Dalton, German Patent 2,255,205 (1973) [*CA* **79**, 31886 (1973)].

⁴⁹⁶ R. H. Linnell, *J. Org. Chem.* **22**, 1691 (1957).

⁴⁹⁷ C. K. McGill, U.S. Patent 4,177,349 (1979) [*CA* **92**, 110871 (1980)].

⁴⁹⁸ M. Tokuyama, *J. Pharm. Soc. Jpn.* **74**, 1404 (1954).

⁴⁹⁹ F. E. Cislak, U.S. Patent 2,992,224 (1961) [*CA* **56**, 461 (1962)].

⁵⁰⁰ V. S. Tsukervanik, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 188 (1969) [*CA* **74**, 125357 (1971)].

⁵⁰¹ F. E. Cislak, U.S. Patent 2,854,457 (1958) [*CA* **53**, 11414 (1959)].

⁵⁰² H. Bonnemann and R. Brinkmann, *Synthesis*, 600 (1975).

⁵⁰³ H. Beschke, H. Friedrich, and H. Offermanns, German Patent 2,639,701 (1978) [*CA* **88**, 169982 (1978)].

⁵⁰⁴ H. Beschke and H. Friedrich, German Patent 2,712,694 (1978) [*CA* **90**, 72061 (1979)].

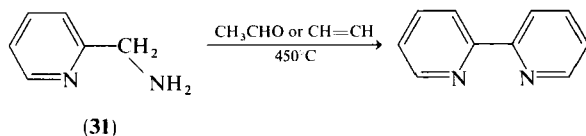
⁵⁰⁵ R. Rehberg and F. Krohnke, *Justus Liebigs Ann. Chem.* **717**, 91 (1968).

⁵⁰⁶ R. L. Frank and E. F. Riener, *J. Am. Chem. Soc.* **72**, 4182 (1950).

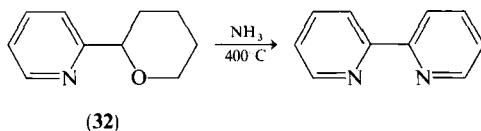
⁵⁰⁷ F. H. Case and W. A. Butte, *J. Org. Chem.* **26**, 4415 (1961).

⁵⁰⁸ L. Proevska, A. Orakhovats, and B. Kurtev, *Izv. Otd. Khim. Nauki, (Bulg. Akad. Nauk.)* **6**, 747 (1973) [*CA* **81**, 3737 (1974)].

synthesis of 2,2':6',2''-terpyridine.⁵⁰⁷ In an interesting related synthesis, pyrolysis of *N,N,N*-trimethylhydrazonium fluoroborates from 2-acetylpyridines affords 2,2':6',2''-terpyridines.⁵⁰⁹ Another development involves conversion of 2-acetylpyridine to 3,3-bis(methylthio)-1-(2-pyridyl)-2-propen-1-one, which on further reaction with 2-acetylpyridine affords 2,6-di(2-pyridyl)-4-(methylthio)pyridine. This compound on refluxing with Raney nickel in ethanol gave 2,2':6',2''-terpyridine. Several related compounds were obtained in the same general way.⁵¹⁰



2-(2-Pyridyl)tetrahydropyran (32), when treated with ammonia over alumina at about 400°C, also gives 2,2'-bipyridine.⁵¹¹ In another related synthesis, the pyrylium salt 4,6-diphenyl-2-(2-pyridinio)pyrylium bis(tetrafluoroborate) was converted to 4,6-diphenyl-2,2'-bipyridine by anhydrous ammonia in ethanol.⁵¹²



Several lithium reagents have been found to convert pyridine to 2,2'-bipyridines in satisfactory yield. Following from the formation of 2,2'-bipyridines from 2-lithiopyridines,⁵¹³⁻⁵¹⁶ it has been found that 2-benzyl-2-lithio-1,3-dithiane forms 2,2'-bipyridine in 30–75% yield when refluxed with pyridine in tetrahydrofuran,^{517,518} and related compounds behave similarly.⁵¹⁹ Lithium diisopropylamide with pyridine in ether affords up to 50% 2,2'-

⁵⁰⁹ G. R. Newkome and D. L. Fishel, *J. Org. Chem.* **37**, 1329 (1972).

⁵¹⁰ K. T. Potts, M. J. Cipullo, P. Ralli, and G. Theodoridis, *J. Am. Chem. Soc.* **103**, 3585 (1981); *J. Org. Chem.* **47**, 3027 (1982).

⁵¹¹ R. D. Bowden, British Patent 1,268,196 (1972) [*CA* **76**, 153616 (1972)].

⁵¹² A. R. Katritzky, E. M. Elisseou, R. C. Patel, and B. Plau, *J. C. S. Perkin I*, 125 (1982).

⁵¹³ C. Osuch and R. Levine, *J. Org. Chem.* **22**, 939 (1957).

⁵¹⁴ H. C. Brown and B. Kanner, *J. Am. Chem. Soc.* **88**, 986 (1966).

⁵¹⁵ E. Deutsch and N. K. V. Cheung, *J. Org. Chem.* **38**, 1123 (1973).

⁵¹⁶ J. E. Parks, B. E. Wagner, and R. H. Holm, *J. Organomet. Chem.* **56**, 53 (1973).

⁵¹⁷ T. Taguchi, M. Nishi, K. Watanabe, and T. Mukaiyama, *Chem. Lett.*, 1307 (1973).

⁵¹⁸ T. Mukaiyama, T. Taguchi, and M. Nishi, Japanese Patent 116,073 (1974) [*CA* **82**, 139965 (1975)].

⁵¹⁹ M. Mukoyama, T. Taguchi, and M. Nishi, Japanese Patent 00,035 (1977) [*CA* **87**, 39296 (1977)].

bipyridine.^{520,521} Similarly, 2,2':6',2''-terpyridine is obtained by reaction of 2,2'-bipyridine with 2-lithiopyridine. A dihydroterpyridine dimer is formed as a by-product.⁵²² 2-Pyridylgold decomposes to 2,2'-bipyridine.⁵²³

A number of minor ways of obtaining 2,2'-bipyridines are worth noting. Irradiation of pyridine with ultraviolet light gives a 1% yield of 2,2'-bipyridine, and 2-picoline likewise affords 6,6'-dimethyl-2,2'-bipyridine,⁵²⁴ whereas γ and X irradiation produces several products including 2,2'-bipyridine.⁵²⁵⁻⁵²⁷ 2,2'-Bipyridine is also obtained by dehydrogenation of 2,2'-bipiperidine,⁵²⁸ whereas substituted 2,2'-bipyridines are formed by dehydrogenation of dihydropyridine dimers.⁵²⁹ 2,2'-Bipyridine is formed in the reaction of styrene tetramer with pyridine,⁵³⁰ by an electrochemical process,⁵³¹ and by the photolysis of metal complexes of picolinic acid.^{532,533} 2,2'-Bipyridine-3,5'-dicarboxylic acid is likewise obtained by photolysis of nicotinic acid in the presence of metal ions.⁵³⁴ 2,2'-Bipyridine is also among the products obtained from the reaction of 2-aminopyridine with isoamyl nitrite.⁵³⁵

Some unusual syntheses of substituted 2,2'-bipyridines deserve mention. Tetracyclone (tetraphenylcyclopentadienone) on heating with picolinonitrile at 215°C affords 3,4,5,6-tetraphenyl-2,2'-bipyridine,⁵³⁶ whereas 5-methyl-2,2'-bipyridine and some polysubstituted 2,2'-bipyridines are obtained by the oxidative degradation of the antibiotic streptonigrin.⁴⁰⁷ 5-Aldehyde-6-amino-2,2'-bipyridines are obtained by acid hydrolysis of pyrido[2,3-*d*]-pyrimidines.^{537,538} In an interesting intramolecular extrusion reaction,

⁵²⁰ A. J. Clarke, S. McNamara, and O. Meth-Cohn, *Tetrahedron Lett.*, 2373 (1974).

⁵²¹ G. R. Newkome and D. C. Hager, *J. Org. Chem.* **47**, 599 (1982).

⁵²² G. R. Newkome, D. C. Hager, and F. R. Fronczek, *J. C. S. Chem. Commun.*, 858 (1981).

⁵²³ L. G. Vaughan, *J. Am. Chem. Soc.* **92**, 730 (1970).

⁵²⁴ K. Pfordte and G. Leuschner, *Justus Liebigs Ann. Chem.* **646**, 30 (1961).

⁵²⁵ F. Antoine, *C. R. Hebd. Seances Acad. Sci.* **258**, 4742 (1964).

⁵²⁶ C. K. Pearce and J. E. Ellison, *J. Phys. Chem.* **70**, 1582 (1966).

⁵²⁷ K. N. Rao and G. Ramanan, *Indian J. Chem.* **6**, 444 (1968).

⁵²⁸ B. Emmert, *Ber. Dtsch. Chem. Ges.* **46**, 1716 (1913).

⁵²⁹ J. P. Kutney, L. Kaczmarek, D. Mostowicz, and B. R. Worth, *Can. J. Chem.* **60**, 323 (1982).

⁵³⁰ K. Yagi, F. Toda, and Y. Iwakura, *J. Polym. Sci., Part B* **10**, 113 (1972).

⁵³¹ R. A. Shaw, German Patent 2,450,100 (1975) [*CA* **83**, 68081 (1975)].

⁵³² T. Kimura, J. Kamimura, K. Takada, and A. Sugimori, *Chem. Lett.*, 237 (1976).

⁵³³ A. Sugimori, K. Takada, T. Kimura, and J. Kamimura, *Bull. Chem. Soc. Jpn.* **54**, 2068 (1981).

⁵³⁴ A. Sugimori, K. Takada, T. Kimura, and J. Kamimura, *Bull. Chem. Soc. Jpn.* **54**, 2070 (1981).

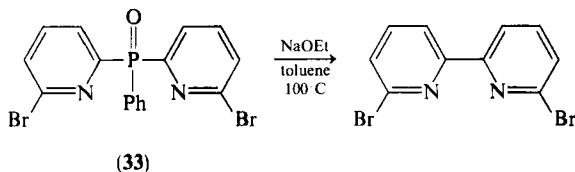
⁵³⁵ P. Hassanaly, G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 461 (1976).

⁵³⁶ T. Jaworski, *Rocz. Chem.* **34**, 899 (1960).

⁵³⁷ G. Evens and P. Caluwe, *J. Org. Chem.* **40**, 1438 (1975).

⁵³⁸ G. Evens and P. Caluwe, *Macromolecules* **12**, 803 (1979).

phosphine oxides such as **33** eliminate the phosphorus entity under the influence of alkali to afford the corresponding 2,2'-bipyridine,⁵³⁹ and related reactions involving the decarbonylation of di(2-pyridyl) ketones also afford 2,2'-bipyridines.⁵⁴⁰ Some work on the biosynthesis of the antibiotic caerulomycin (**7**) has been reported. The complete pathway has not been elucidated, but it is known that lysine is a precursor of the unsubstituted ring.⁵⁴¹



To complete the section on the synthesis of 2,2'-bipyridines, we note a number of ways of preparing hydroxybipyridines and bipyridinones. Condensation of enamine ketones such as **34** with dimeric malononitrile (**35**) affords substituted 2,2'-bipyridinediones of type **36**. The reaction mechanism is similar to that of the Ritter reaction.⁵⁴²⁻⁵⁴⁴ Condensation of 1-(ethoxycarbonylmethyl)pyridinium bromide (**37**) with 2-(*p*-nitrobenzylideneacetyl)-pyridine (**38**) and ammonium acetate affords the bipyridinone **39**.⁵⁴⁵ This method has subsequently been extended to the preparation of several substituted 2,2'-bipyridines and oligopyridines^{273,546,547} from appropriate acylalkylpyridinium salts and unsaturated aldehydes and ketones. Oxidation of 5-hydroxy-2-pyridone with peroxidase and hydrogen peroxide gives the dihydroxybipyridinedione **40**,⁵⁴⁸ whereas oxidative coupling of 3-hydroxypyridines with PbO₂ likewise affords 3,3'-dihydroxy-2,2'-bipyridines, which have a strong green fluorescence.^{549,550} 2,6-Di(2-pyridyl)-4-pyridones such as **41** are readily obtained by dehydrogenation of the corresponding 4-piperidones.⁵⁵¹

⁵³⁹ G. R. Newkome and D. C. Hager, *J. Am. Chem. Soc.* **100**, 5567 (1978).

⁵⁴⁰ G. R. Newkome and H. C. R. Taylor, *J. Org. Chem.* **44**, 1362 (1979).

⁵⁴¹ A. G. McInnes, D. G. Smith, J. A. Walter, L. C. Vining, and J. L. C. Wright, *Can. J. Chem.* **57**, 3200 (1979).

⁵⁴² H. Junek, H. Sterk, and A. Schmidt, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **21B**, 1145 (1966).

⁵⁴³ H. Junek and A. Schmidt, *Monatsh. Chem.* **99**, 635 (1968).

⁵⁴⁴ H. Junek and G. Stolz, *Monatsh. Chem.* **101**, 1234 (1970).

⁵⁴⁵ F. Kroehnke, K. E. Schnalke, and W. Zecher, *Chem. Ber.* **103**, 322 (1970).

⁵⁴⁶ F. Kroehnke, *Synthesis*, 1 (1976).

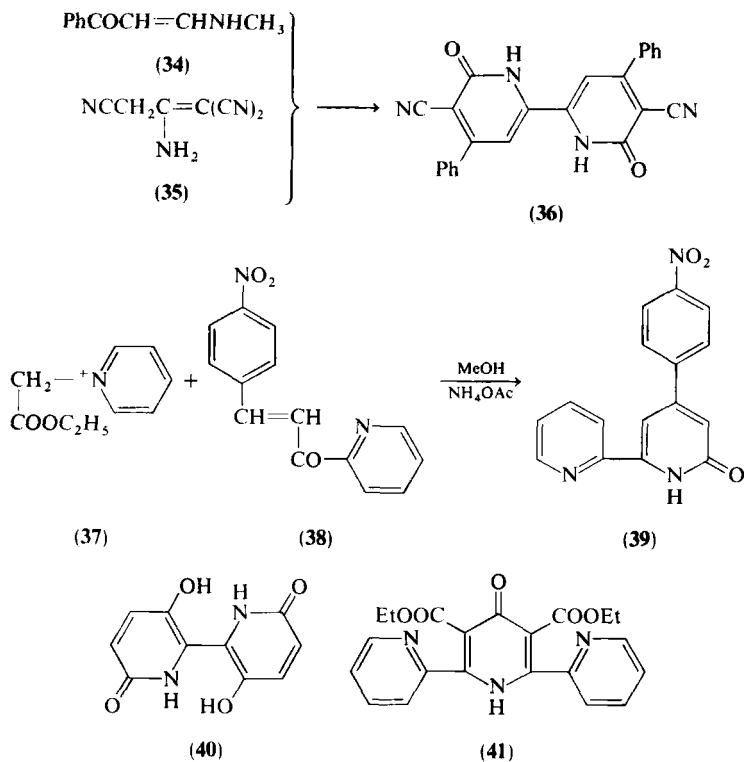
⁵⁴⁷ R. M. Propst and L. S. Trzupek, *J. Am. Chem. Soc.* **103**, 3233 (1981).

⁵⁴⁸ H. Loth and K. Eichner, *Arch. Pharm. (Weinheim, Ger.)* **302**, 264 (1969).

⁵⁴⁹ J. G. Wirth, U.S. Patent 3,676,448 (1972) [*CA* **77**, 103415 (1972)].

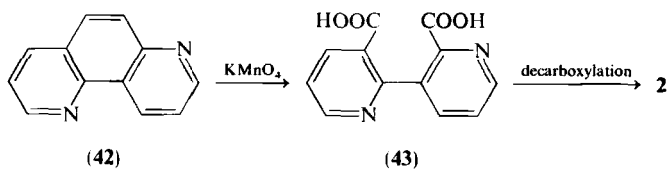
⁵⁵⁰ J. Rebek and R. V. Wattley, *J. Heterocycl. Chem.* **17**, 749 (1980).

⁵⁵¹ K. W. Merz and R. Haller, *Arch. Pharm. (Weinheim, Ger.)* **296**, 134 (1963).



B. 2,3'-BIPYRIDINE

2,3'-Bipyridine was first prepared one hundred years ago by the permanganate oxidation of 1,7-phenanthroline (**42**) to the dicarboxylic acid **43**, followed by decarboxylation.⁵⁵² Modifications of this method have been used.^{95,96,553,554} 2,3'-Bipyridine is among the products obtained from



⁵⁵² Z. H. Skrap and G. Vortmann, *Monatsh. Chem.* **3**, 570 (1882).

⁵⁵³ C. Schopf, A. Komzak, F. Braun, E. Jacobi, M. L. Bormuth, M. Bullnheimer, and I. Hagel, *Justus Liebigs Ann. Chem.* **559**, 1 (1948).

⁵⁵⁴ R. Lukes and J. Pliml, *Chem. Listy* **49**, 1836 (1955).

the thermal dehydrogenation and pyrolysis of pyridine along with other bipyridines, but the yield is not high^{426,427} even in the presence of ferric chloride as catalyst.⁸⁵ A common route to 2,3'-bipyridine, however, involves dehydrogenation of the alkaloid anabasine (**12**: R = H). A variety of dehydrogenating agents assist in the process.^{21,75,555-563} 2,3'-Bipyridine is also formed during the sulfonation⁵⁶³⁻⁵⁶⁵ and bromination⁵⁶⁶⁻⁵⁶⁸ of anabasine, isoanabasine [3-(2-pyridyl)piperidine] and 2,3'-bipiperidine. Sometimes polypyridines are isolated as by-products.⁵⁶⁵ Anabasine 1-oxide⁵⁶⁹ and the natural products anatabine (**13**: R = H),^{33,34} ammodendrine (**16**: R = CH₃, R' = H),⁴⁴ and adenocarpine (**16**: R = CH=CHPh, R' = H)^{60,570} are likewise dehydrogenated to 2,3'-bipyridine, and related dehydrogenation reactions afford substituted 2,3'-bipyridines.⁵⁷¹ Ullmann and Grignard reactions have been used to synthesise 2,3'-bipyridine,^{425,572} whereas the Gomberg reaction of 3-pyridinediazonium chloride with pyridine and alkyl pyridines affords 2,3'-bipyridine, along with other isomeric bipyridines, and alkyl substituted 2,3'-bipyridines, respectively.^{15,573,574} Photolysis of 3-

⁵⁵⁵ B. M. Dubinin and G. V. Chelintsev, *J. Gen. Chem. USSR (Engl. Transl.)* **16**, 105 (1946).

⁵⁵⁶ A. S. Sadykov and O. S. Otroshchenko, U.S.S.R. Patent 108,301 (1957) [*CA* **52**, 11960 (1958)].

⁵⁵⁷ Y. V. Kurbatov, A. S. Kurbatova, O. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 9 (1969); [*CA* **74**, 142111 (1971)].

⁵⁵⁸ E. Leete, *J. Am. Chem. Soc.* **91**, 1697 (1969).

⁵⁵⁹ Y. V. Kurbatov, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 185 (1969) [*CA* **75**, 48837 (1971)].

⁵⁶⁰ Y. V. Kurbatov, A. S. Kurbatova, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 9 (1969) [*CA* **75**, 35646 (1971)].

⁵⁶¹ S. V. Zalyalieva, Y. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and R. Azzamova, *Khim. Geterotsikl. Soedin.*, 816 (1973).

⁵⁶² R. D. Bowden, British Patent 1,268,192 (1972) [*CA* **76**, 153605 (1972)].

⁵⁶³ A. S. Sadykov, O. S. Otroshchenko, and T. K. Yunusov, *Pol. J. Chem.* **53**, 367 (1979).

⁵⁶⁴ O. S. Otroshchenko and A. S. Sadykov, *Zh. Obshch. Khim.* **24**, 1685 (1954).

⁵⁶⁵ T. K. Yunusov, K. Akbarov, and O. S. Otroshchenko, *Uzb. Khim. Zh.*, 77 (1980) [*CA* **93**, 168454 (1980)].

⁵⁶⁶ A. S. Sadykov, O. S. Otroshchenko, and V. K. Kiryukhin, *Zh. Obshch. Khim.* **34**, 4127 (1964).

⁵⁶⁷ O. S. Otroshchenko, A. S. Sadykov, and V. K. Kiryukhin, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **263**, 24 (1964) [*CA* **63**, 3007 (1965)].

⁵⁶⁸ O. S. Otroshchenko, A. S. Sadykov, V. K. Kiryukhin, M. Goshayev, and L. Srybnaya, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 104 (1969) [*CA* **74**, 31878 (1971)].

⁵⁶⁹ Y. V. Kurbatov, A. S. Kurbatova, G. Y. Markeeva, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 3 (1969) [*CA* **73**, 120465 (1970)].

⁵⁷⁰ I. Ribas, *Rev. R. Acad. Cienc. Exactas, Fis. Nat. Madrid* **54**, 405 (1960).

⁵⁷¹ H. Beyer and K. Leverenz, *Chem. Ber.* **94**, 407 (1961).

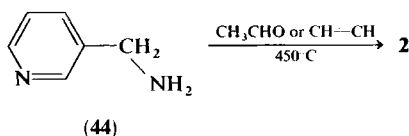
⁵⁷² M. Goshayev, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 95 (1969) [*CA* **74**, 53433 (1971)].

⁵⁷³ R. Lukes and J. Pliml, *Chem. Listy* **52**, 759 (1958).

⁵⁷⁴ R. L. Frank and J. V. Crawford, *Bull. Soc. Chim. Fr.*, 419 (1958).

pyridinediazonium chloride in pyridine likewise affords 2,3'-bipyridine (and 3,3'-bipyridine), and irradiation of related triazenes gives some 2,3'-bipyridines as well.^{575,576}

As in the synthesis of 2,2'-bipyridines, several routes are available for the preparation of 2,3'-bipyridines, where one of the pyridine rings is built up from simpler entities. Thus 3-(aminomethyl)pyridine (**44**) with acetaldehyde



or acetylene at 450°C affords 2,3'-bipyridine,⁵⁰¹ whereas 3-cyanopyridine reacts with acetylene at 120°C in the presence of a cobalt catalyst to give 2,3'-bipyridine in over 90% yield.⁵⁰² 3-Acetylpyridine with acrolein and ammonia in the presence of dehydrating and dehydrogenating catalysts also gives 2,3'-bipyridine.⁵⁰³ Earlier related syntheses afforded, for example, 2,6-di(3-pyridyl)-4-phenylpyridine from the condensation of benzaldehyde with 2 moles of 3-acetylpyridine in the presence of ammonium hydroxide and ammonium acetate.⁵⁰⁶ 2,4-Di(3-pyridyl)pyridine was thought similarly to be formed from 3-acetylpyridine, formaldehyde, and ammonium acetate,¹⁷ but the product was later shown to be a mixture.¹⁶ Irradiation of pyridine with γ and X rays leads to the formation of some 2,3'-bipyridine along with several other products.⁵²⁶ The biosynthesis of 2,3'-bipyridine is thought to be accomplished from nicotinic acid possibly by way of anatabine (**13**: R = H).⁵⁷⁷ It has been suggested that 2,3'-bipyridine is an artifact produced by oxidation of anatabine (**13**: R = H).²⁷⁹

A number of syntheses of substituted 2,3'-bipyridines are worthy of note. Tetracyclone heated at 215°C with nicotinonitrile affords 3,4,5,6-tetraphenyl-2,3'-bipyridine,⁵³⁶ whereas 3,4-di(2-pyridyl)pyridine is obtained by an oxidative degradation of the corresponding 6,7-disubstituted thiazolo[3,2-*a*]-pyridinium salt.⁵⁷⁸ Nicotinic acid on UV irradiation in aqueous solution at pH 4–6 gives 2,3'-bipyridine-5-carboxylic acid,⁵⁷⁹ whereas irradiation of picolinic acid in the same pH range in the absence of metal ions gives some 2,3'-bipyridine.⁵³³ 6,6'-Diphenyl-2,3'-bipyridine is thought to be formed from

⁵⁷⁵ I. Szczerek and P. Nantka-Namirski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **19**, 457 (1971).

⁵⁷⁶ M. Julliard, M. Scelles, A. Guillemonat, G. Vernin, and J. Metzger, *Tetrahedron Lett.*, 375 (1977).

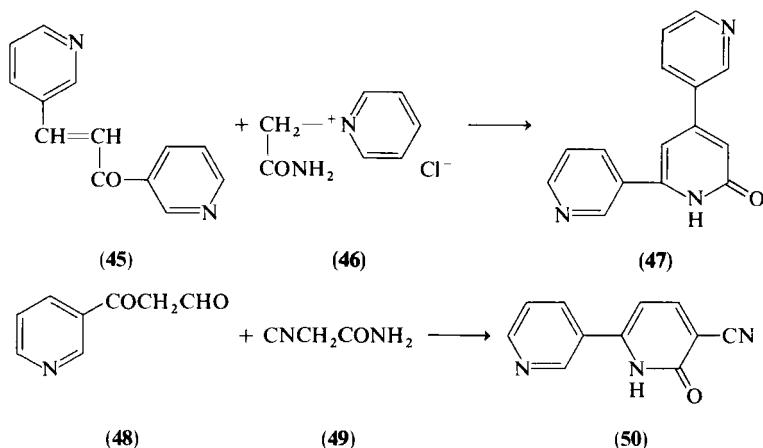
⁵⁷⁷ E. Leete and S. A. Slattery, *J. Am. Chem. Soc.* **98**, 6326 (1976).

⁵⁷⁸ O. Westphal, G. Feix, and A. Joos, *Angew. Chem., Int. Ed. Engl.* **8**, 74 (1969).

⁵⁷⁹ F. Takeuchi, T. Sugiyama, T. Fujimori, K. Seki, Y. Harada, and A. Sugimori, *Bull. Chem. Soc. Jpn.* **47**, 1245 (1974).

2-phenylpyridine and its lithio derivative,⁵⁸⁰ whereas 2',5,5',6,6'-pentachloro-4,4'-bis(dimethylamino)-2,3'-bipyridine is one of the products formed from the reaction of 2,3,5,6-tetrachloro-4-dimethylaminopyridine with butyllithium.⁵⁸¹ A Diels–Alder oxazole reaction, more fully illustrated in Section III,C has been applied to the preparation of substituted 2,3'-bipyridines.⁵⁸² A bis-2,3'-bipyridine sulfide is thought to be among the products of the dehydrogenation of anabasine with sulfur.⁵⁶³

Several condensation routes to 2,3'-bipyridinones have been reported. Thus 3-acetylpyridine and nicotinaldehyde were condensed to the α,β -unsaturated ketone **45**, which reacted in a Michael condensation with 1-(carbamoylmethyl)pyridinium chloride (**46**) to give 2,4-di(3-pyridyl)-6-pyridone (**47**). Compound **47** was converted to the alkaloid nicotelline **10** by replacement of the hydroxyl group of **47** by chlorine, followed by reductive dehalogenation.^{18,583–585} Related condensations have been described,⁵⁴⁵ including the synthesis of 4,6-diphenyl-2,3'-bipyridine.⁵⁴⁶ Similarly, aldehyde **48** was condensed with cyanoacetamide (**49**) to afford 2-(3-pyridyl)-5-cyano-6-pyridone (**50**), the cyano group of which was hydrolyzed and decarboxylated to 2,3'-bipyridin-6-one.⁵⁸⁶ Several modifications and extensions of



⁵⁸⁰ C. S. Giam, E. E. Knaus, and F. M. Pasutto, *J. Org. Chem.* **39**, 3565 (1974).

⁵⁸¹ J. D. Cook and B. J. Wakefield, *J. Chem. Soc. C*, 1973 (1969).

⁵⁸² P. B. Terent'ev, N. P. Lomakina, M. I. Rahimi, K. D. Riad, Y. B. Zelikhov, and A. N. Kost, *Khim. Geterotsikl. Soedin*, 1255 (1980).

⁵⁸³ J. Thesing, U.S. Patent 2,909,529 (1959) [*CA* **54**, 2370 (1960)].

⁵⁸⁴ J. Thesing and A. Muller, *Chem. Ber.* **90**, 711 (1957).

⁵⁸⁵ J. Thesing, German Patent 1,092,016 (1960) [*CA* **55**, 19957 (1961)].

⁵⁸⁶ G. Y. Leshner and M. D. Gruett, German Patent 2,125,310 (1972) [*CA* **78**, 58383 (1973)].

these cyanoacetamide condensations have been described.⁵⁸⁷⁻⁵⁹⁰ Hydrolysis of oxazine derivatives affords a route to certain substituted 2,3'-bipyridinones.⁵⁹¹ Dehydrogenation of piperidones analogous to compound **41** affords 2,3'-bipyridinone derivatives.⁵⁵¹

C. 2,4'-BIPYRIDINE

2,4'-Bipyridine was probably first prepared in 1886 as one of the products of the pyrolysis of pyridine,⁵⁹² although it was not considered as such until much later.⁴²⁶ Isomeric bipyridines and several other products are formed as well in the process.^{85,90,429} It is also formed along with 2,2'-bipyridine by the pyrolysis of metal salts of picolinic acid.⁴⁰¹ 2,4'-Bipyridine (**3**) is, however, obtained free of other isomers from 1,8-phenanthroline by permanganate oxidation, followed by decarboxylation of the resultant dicarboxylic acid,⁹¹ and by an Ullmann reaction from 2-bromopyridine and 4-chloropyridine along with 2,2'- and 4,4'-bipyridines.^{414,593} 3,3'-Dinitro-2,4'-bipyridine is one of the products obtained similarly from a mixture of 2- and 4-chloro-3-nitropyridines under Ullmann conditions.⁴²² 2,4'-Bipyridine is also one of the bipyridines formed by the reaction of an alkali metal, such as sodium or magnesium, with pyridine, although 4,4'-bipyridine is the predominant isomer formed, and by the reaction of pyridine 1-oxide with pyridine in the presence of sodium.⁴⁹⁹ However, a difluoro-2,4'-bipyridine is among the products of the reaction of 3-fluoropyridine with potassium amide in liquid ammonia.⁵⁹⁴

Like 2,2'- and 2,3'-bipyridines, 2,4'-bipyridine is formed by a number of reactions where one of the pyridine rings is built up from simpler components. Thus 4-(aminomethyl)pyridine with acetylene or acetaldehyde at 450°C affords 2,4'-bipyridine⁵⁰¹ and 4-cyanopyridine reacts with acetylene at 120°C under pressure in the presence of a cobalt catalyst to give 2,4'-bipyridine in over 90% yield.⁵⁰² 4-Acetylpyridine with acrolein and ammonia in the presence of dehydrating and dehydrogenating catalysts also gives 2,4'-bipyridine.⁵⁰³ A number of minor routes to 2,4'-bipyridine are worthy of

⁵⁸⁷ R. R. Rastogi, H. Ila, and H. Junjappa, *J. C. S. Chem. Commun.*, 645 (1975).

⁵⁸⁸ G. Y. Leshner and C. J. Opalka, U.S. Patent 4,004,012 (1977) [*CA* **86**, 189725 (1977)].

⁵⁸⁹ P. Nantka-Namirski and L. Kaczmarek, *Acta Pol. Pharm.* **34**, 133 (1977).

⁵⁹⁰ R. R. Rastogi, A. Kumar, H. Ila, and H. Junjappa, *J. C. S. Perkin I*, 549 (1978).

⁵⁹¹ T. Kato and M. Kondo, *Chem. Pharm. Bull.* **24**, 356 (1976).

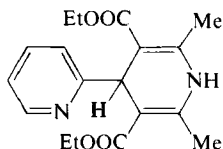
⁵⁹² C. F. Roth, *Ber. Dtsch. Chem. Ges.* **19**, 360 (1886).

⁵⁹³ O. S. Otroshchenko, M. Goshayev, A. S. Sadykov, and N. V. Kuznetsova, U.S.S.R. Patent 253,066 (1969) [*CA* **72**, 121372 (1970)].

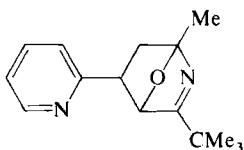
⁵⁹⁴ R. J. Martens, H. J. den Hertog, and M. van Ammers, *Tetrahedron Lett.*, 3207 (1964).

mention. It is formed by dehydrogenation of 2,4'-bipiperidine,⁵⁹⁵ in low yield by the reaction of pyridine 1-oxide with acetic anhydride⁵⁹⁶ along with 2,2'- and 4,4'-bipyridines from a high-temperature catalyzed reaction of an acrolein dimer with methanol and ammonia⁵⁹⁷ and by irradiation of pyridine.^{526,527}

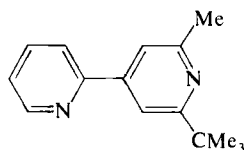
A number of syntheses of substituted 2,4'-bipyridines have been described. Thus condensation of pyridine-2-aldehyde with ethyl β -aminocrotonate gave the dihydro-2,4'-bipyridine **51**, which after oxidation, hydrolysis, and decarboxylation, affords 2',6'-dimethyl-2,4'-bipyridine. This compound on further oxidation and decarboxylation gave 2,4'-bipyridine.⁸⁹ The Hantzsch reaction applied to pyridine-2-aldehyde, ethyl acetoacetate, and ammonia also gives compound **51**.⁹¹ Related syntheses have been reported,^{598,599} some of which lead to the parent 2,4'-bipyridine.⁶⁰⁰ A similar condensation applied to ethyl isonicotinoylacetate, formalin, and hydroxylamine affords 2,6-di(4-pyridyl)-pyridine.⁶⁰¹ The Diels-Alder intermediate formed by reaction of a 2-vinylpyridine with substituted oxazoles undergoes aromatization and dehydration to 2,4'-bipyridines. For example, the intermediate **52** gives compound **53**.^{582,602-604} Several other routes to specific substituted



(51)



(52)



(53)

2,4'-bipyridines deserve mention. Thus isonicotinonitrile and tetracyclone heated at 215°C afford 3,4,5,6-tetraphenyl-2,4'-bipyridine.⁵³⁶ 3',5-Di(2-piperidyl)-2,4'-bipyridine is obtained from anabasine (**12**; R = H) by a dehydrogenation condensation with sodium,⁶⁰⁵ whereas photolysis of

⁵⁹⁵ E. P. Hart, *J. Chem. Soc.*, 3872 (1953).

⁵⁹⁶ D. M. Pretorius and P. A. de Villiers, *J. S. Afr. Chem. Inst.* **18**, 48 (1965).

⁵⁹⁷ A. Campbell, I. Campbell, and J. A. Corran, British Patent 1,020,856 (1966) [*CA* **64**, 15852 (1966)].

⁵⁹⁸ P. Nantka-Namirski and R. Balicki, *Acta Pol. Pharm.* **31**, 279 (1974).

⁵⁹⁹ R. Balicki, H. Blaszcak, and P. Nantka-Namirski, *Acta Pol. Pharm.* **37**, 1 (1980).

⁶⁰⁰ R. Balicki, L. Kaczmarek, and P. Nantka-Namirski, *Pol. J. Chem.* **53**, 893 (1979).

⁶⁰¹ O. Y. Magidson, *Zh. Obshch. Khim.* **29**, 165 (1959).

⁶⁰² P. B. Terent'ev, M. Islam, A. A. Zaitsev, and A. N. Kost, *Vestn. Mosk. Univ., Ser. 2: Khim.* **24**, 123 (1969) [*CA* **71**, 12970 (1969)].

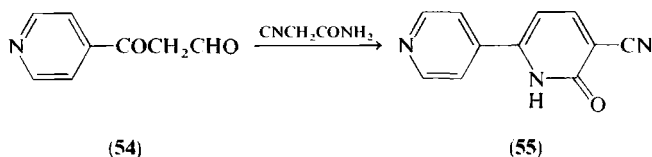
⁶⁰³ A. N. Kost, P. B. Terent'ev, M. Islam, and A. A. Zaitsev, U.S.S.R. Patent 250,142 (1969) [*CA* **72**, 78883 (1970)].

⁶⁰⁴ P. B. Terent'ev, M. Islam Rahimi, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1323 (1979).

⁶⁰⁵ A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, V. I. Akhmedzhanova, and G. A. Tolkaecheva, *Khim. Geterotsikl. Soedin.*, 1076 (1973).

2-cyanopyridine affords 2'-cyano-2,4'-bipyridine.⁶⁰⁶ Condensation of pyridine-2-aldehyde with a 1-(benzoylmethyl)pyridinium salt, ω -methoxyacetophenone, and ammonia gives 2',6'-diphenyl-3'-methoxy-2,4'-bipyridine,⁶⁰⁷ and some 2',6'-diphenyl-2,4'-bipyridines are also obtained by condensation of *N*-pyridinium phenacylides with 2-pyridylideneacetophenone in the presence of ammonium acetate.⁶⁰⁸ Related condensations have been described.⁵⁴⁶

To conclude the section on the syntheses of 2,4'-bipyridines, we cover the syntheses of 2,4'-bipyridinones. Condensation of the aldehyde **54** with cyanoacetamide affords the cyano-substituted 2,4'-bipyridin-6-one **55**, the cyano group of which may be removed by hydrolysis and decarboxylation.⁵⁸⁶ Several related cyanoacetamide condensations have been reported.^{589,590,609-611} Dehydrogenation of piperidones analogous to compound **41** affords 2,4'-bipyridinone derivatives.⁵⁵¹



D. 3,3'-BIPYRIDINE

3,3'-Bipyridine (**4**) was first prepared in 1883 by the permanganate oxidation of 4,7-phenanthroline, followed by decarboxylation of the resultant dicarboxylic acid.⁹⁷ Chromium trioxide may be used in the oxidation step.⁶¹² This method, sometimes with modifications, has been used on several occasions to prepare 3,3'-bipyridine^{80,92,96,613} and substituted 3,3'-bipyridines from the appropriate 4,7-phenanthroline^{614,615} or 5,6-dihydro-4,7-phenanthroline.⁶¹⁶ Closely related syntheses include the formation of

⁶⁰⁶ Y. Ito and T. Matsuura, *J. Org. Chem.* **44**, 41 (1979).

⁶⁰⁷ H. J. Teuber, G. Schutz, and H. J. Bader, *Justus Liebigs Ann. Chem.*, 1321 (1977).

⁶⁰⁸ P. S. Kendurkar and R. S. Tewari, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **29B**, 552 (1974).

⁶⁰⁹ G. Y. Leshner and M. D. Gruett, French Patent 2,138,216 (1973) [*CA* **79**, 32022 (1973)].

⁶¹⁰ G. Y. Leshner and M. D. Gruett, British Patent 1,322,318 (1973) [*CA* **79**, 105231 (1973)].

⁶¹¹ R. Balicki and P. Nantka-Namirski, *Pol. J. Chem.* **53**, 2121 (1979).

⁶¹² A. Kaufmann and R. Radosevic, *Ber. Dtsch. Chem. Ges.* **42**, 2612 (1909).

⁶¹³ R. L. Williams and M. G. El Fayoumy, *J. Heterocycl. Chem.* **9**, 1021 (1972).

⁶¹⁴ E. H. Woodruff and R. Adams, *J. Am. Chem. Soc.* **54**, 1977 (1932).

⁶¹⁵ G. Jacini and A. Salini, *Gazz. Chim. Ital.* **69**, 717 (1939).

⁶¹⁶ A. L. Searles and R. M. Warren, *J. Org. Chem.*, **18**, 1317 (1953).

2,2'-diacetyl-3,3'-bipyridines by the lead acetate oxidation of 5,6-dimethyl-5,6-dihydroxy-5,6-dihydro-4,7-phenanthroline⁶¹⁷ and the formation of a substituted 3,3'-bipyridine by reaction of 4,7-phenanthroline-5,6-dione with ammonium acetate and acetic acid.⁶¹⁸ 3-Bromopyridine self-couples with loss of halogen on reaction with hydrazine, a palladium catalyst, and potassium hydroxide to afford 3,3'-bipyridine, whereas 3,5-dibromopyridine gives, among others, 3,3'-bipyridine and 3,5-di(3-pyridyl)pyridine.⁶¹⁹ 3,3'-Bipyridine is also obtained from 3-bromopyridine under Ullmann-type reaction conditions although, not unexpectedly, the halogen in 3-bromopyridine is less reactive than in 2- or 4-bromopyridine.^{425,620} Some symmetrically substituted 3,3'-bipyridines are likewise formed from substituted 3-halopyridines.⁶²¹⁻⁶²⁴ Tetrachloro-5-iodopyridine under Ullmann conditions affords octachloro-3,3'-bipyridine,⁶²⁵ and 3,5-dichlorotrifluoropyridine gives 5,5'-dichlorohexafluoro-3,3'-bipyridine.⁶²⁵ 3,3'-Bipyridine is formed in small amounts with other isomeric bipyridines by the pyrolysis of pyridine,^{85,427} whereas 2,4,6-collidine affords a hexamethyl-3,3'-bipyridine.⁴²⁶ 3,3'-Bipyridine is one of the minor products obtained by the reaction of pyridine with sodium.⁶²⁶ It is also formed from 3-pyridine diazonium salts in a Gomberg-type reaction with pyridine along with 2,3'-bipyridine and other products.⁵⁷³⁻⁵⁷⁵ 4-Methyl-3,3'-bipyridine is formed when 4-picoline is used instead of pyridine in this reaction.¹⁵ Decomposition of related triazenes gives some 3,3'-bipyridine as well,^{535,575} Dry distillation of pyridine-3-sulfonic acid is another route to 3,3'-bipyridine.⁶²⁷

A few syntheses of specific substituted 3,3'-bipyridines have been reported. 6,6'-Dialkyl-3,3'-bipyridines have been shown to be one of the products of the reaction of 1-lithio-2-alkyl-1,2-dihydropyridines with perhalomethanes,⁶²⁸ cyanogen bromide,⁶²⁹ or bromine.⁶³⁰ In an interesting double

⁶¹⁷ B. Eistert and G. Fink, *Chem. Ber.* **95**, 2395 (1962).

⁶¹⁸ B. Dash, E. K. Dora, and C. S. Panda, *J. Indian Chem. Soc.* **56**, 1017 (1979).

⁶¹⁹ M. Busch, W. Weber, C. Darboven, W. Renner, H. J. Hahn, G. Mathauser, F. Stratz, K. Zittmann, and H. Engelhardt, *J. Prakt. Chem.* **146**, 1 (1936).

⁶²⁰ G. Gall, K. Honty, G. Kalas, and C. Szantay, Hungarian Patent 17,177 (1979) [*CA* **92**, 181024 (1980)].

⁶²¹ W. D. Jones, G. L. Jenkins, and J. E. Christian, *J. Am. Pharm. Assoc.* **38**, 70 (1949).

⁶²² H. C. Fielding, British Patent 1,085,882 (1967) [*CA* **67**, 117564 (1967)].

⁶²³ R. D. Chambers, D. Lomas, and W. K. R. Musgrave, *J. Chem. Soc. C*, 625 (1968).

⁶²⁴ N. S. Bazhenova, Y. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and S. Kim, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **206**, 241 (1972) [*CA* **80**, 36965 (1974)].

⁶²⁵ A. G. Mack, H. Suschitzky, and B. J. Wakefield, *J. C. S. Perkin I*, 1682 (1980).

⁶²⁶ C. R. Smith, *J. Am. Chem. Soc.* **46**, 414 (1924).

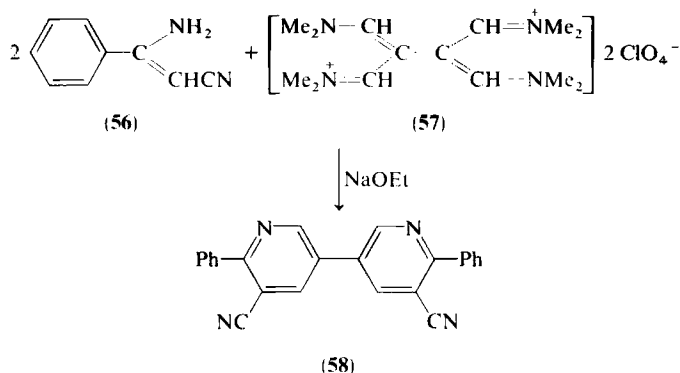
⁶²⁷ T. Leone and V. Oliveri, *Gazz. Chim. Ital.* **15**, 274 (1885).

⁶²⁸ C. S. Giam, E. E. Knaus, R. A. Lockhart, and I. G. Keener, *Can. J. Chem.* **53**, 2305 (1975).

⁶²⁹ E. E. Knaus, T. A. Ondrus, and C. S. Giam, *J. Heterocycl. Chem.* **13**, 789 (1976).

⁶³⁰ R. F. Francis, C. D. Crews, and B. S. Scott, *J. Org. Chem.* **43**, 3227 (1978).

pyridine ring closure, the salt **57** condensed with 2 moles of β -aminocinnamionitrile (**56**) to afford 5,5'-dicyano-6,6'-diphenyl-3,3'-bipyridine (**58**).⁶³¹ The Diels-Alder oxazole reaction referred to in the synthesis of 2,4'-bipyridines has been applied to the preparation of substituted 3,3'-bipyridines.⁵⁸² In an unusual synthesis, a 6,6'-disubstituted 3,3'-bipyridine is among the products of the radical alkylation of pyridine with 2-methyl-3,3-pentamethyleneoxazirane.⁶³²



There has been considerable interest in hydroxy-3,3'-bipyridines and 3,3'-bipyridinones. Following from some very early work on the oxidation of citrazinic acid (2,6-dihydroxypyridine-4-carboxylic acid),⁶³³ which was considered to give some polyhydroxy-3,3'-bipyridines, it has been shown that the 3,3'-bipyridinone **59**, a product of the hydrolysis of a natural blue pigment from *Corynebacterium insidiosum*, is obtained by oxidation of 2-hydroxy-5-aminopyridine (**60**) or 2,6-dihydroxypyridine-4-carboxylic acid (**61**).^{80,83} A similar oxidation of 2,6-dihydroxy-3-aminopyridine-4-carboxylic acid affords the natural product indigoidine (**20**).⁸⁰ Numerous related oxidative condensations have been reported subsequently.^{80,548,634-638} Cyanoacetamide condensations analogous to those discussed in the synthesis of 2,3'-bipyridines afford, for example, the cyano-substituted 3,3'-bipyridinone **62**,⁵⁸⁸ whereas condensation of 3-pyridylacetonitrile with ethyl phenylpropiolate and ethanol affords compound **63**.⁶³⁹ To complete the section on

⁶³¹ J. E. A. Otterstedt and R. Pater, *J. Heterocycl. Chem.* **9**, 225 (1972).

⁶³² F. Minisci, R. Galli, V. Malatesta, and T. Caronna, *Tetrahedron* **26**, 4083 (1970).

⁶³³ W. J. Sell and H. Jackson, *J. Chem. Soc.* **75**, 507 (1899).

⁶³⁴ H. J. Knackmuss, *Chem. Ber.* **101**, 1148 (1968).

⁶³⁵ H. J. Knackmuss, *Chem. Ber.* **101**, 2679 (1968).

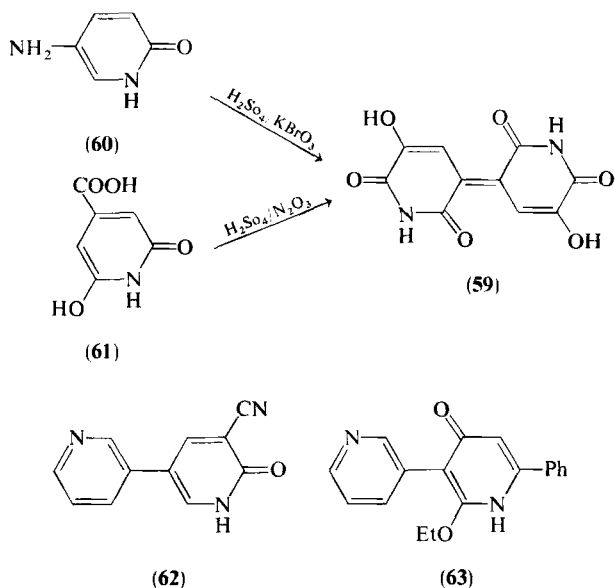
⁶³⁶ P. Nantka-Namirski and A. Rykowski, *Acta Pol. Pharm.* **31**, 433 (1974).

⁶³⁷ P. Nantka-Namirski and A. Rykowski, *Acta Pol. Pharm.* **33**, 13 (1976).

⁶³⁸ K. Krowicki, *Rocz. Chem.* **51**, 1035 (1977).

⁶³⁹ H. N. Al-Jallo and F. Al-Azawi, *J. Heterocycl. Chem.* **14**, 27 (1977).

the synthesis of 3,3'-bipyridines, we record the interesting rearrangement of 1-(4'-pyridyloxy)-4-pyridone to 4,4'-dihydroxy-3,3'-bipyridine, which after treatment with phosphorus halides was reductively dehalogenated to 3,3'-bipyridine.⁶⁴⁰

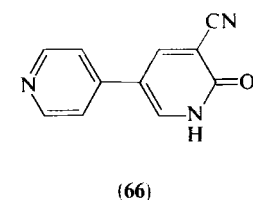
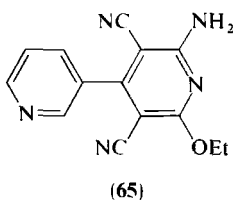
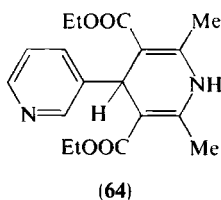


E. 3,4'-BIPYRIDINE

Although 3,4'-bipyridine was considered to be one of the bipyridines produced by the reaction of pyridine with sodium⁶²⁶ or by the pyrolysis of pyridine in the presence of ferric chloride,⁸⁵ there is considerable doubt about the authenticity of the 3,4'-bipyridine produced in these cases. Authentic 3,4'-bipyridine, however, was isolated in 1950 from the products of the pyrolysis of pyridine at 850°C.^{90,427} Its structure was confirmed by synthesis involving the condensation of pyridine-3-aldehyde and ethyl β -aminocrotonate to give the dihydro-3,4'-bipyridine **64**. This compound on oxidation, hydrolysis, and decarboxylation gave 2',6'-dimethyl-3,4'-bipyridine, which on further oxidation and decarboxylation gave 3,4'-bipyridine.⁸⁹ Acetoacetic ester and ammonia may be used in the condensation

⁶⁴⁰ T. Kosuge, H. Zenda, and Y. Suzuki, *Chem. Pharm. Bull.* **18**, 1068 (1970).

instead of ethyl β -aminocrotonate.⁶⁴¹ Several related condensations have subsequently been reported.^{598 600} 3-Picolylidenepyruvic acid and the pyridinium bromide salt that is obtained from pyridine and ethyl bromopyruvate condense together in the presence of ammonium acetate to afford 2',6'-diethoxycarbonyl-3,4'-bipyridine, which after hydrolysis and decarboxylation provides another route to 3,4'-bipyridine,²¹¹ whereas a mixture of pyridine-3-aldehyde, acetaldehyde, ammonia, and ammonium acetate heated to 250°C also affords some 3,4'-bipyridine.⁶⁴² In a similar way, reaction of pyridine-3-aldehyde with 2 mol of malononitrile and excess sodium alkoxide gives, for example, the dicyanosubstituted 3,4'-bipyridine **65**.⁶⁴³⁻⁶⁴⁵



A few other syntheses of substituted 3,4'-bipyridines have been reported. The Diels–Alder oxazole reaction referred to in the synthesis of 2,4'-bipyridines has been similarly applied to the preparation of some substituted 3,4'-bipyridines.^{582,602,603} In an interesting example involving a bromine migration, interaction of 3-bromo-2-chloropyridine and butyllithium gives 2,2'-dichloro-4-bromo-3,4'-bipyridine.⁶⁴⁶ Condensation of pyridine-3-aldehyde with a 1-(benzoylmethyl)pyridinium salt, ω -methoxyacetophenone, and ammonia gives 2,6-diphenyl-3-methoxy-4-(3-pyridyl)pyridine.⁶⁰⁷ Reaction of pyrylium salts with acetic acid and ammonium acetate provides another interesting route to 3,4'-bipyridine derivatives.^{647,648} Octachloro-3,4'-bipyridine is thought to be a by-product of the reaction of 4-bromotetrachloropyridine with copper under Ullmann conditions.⁶²⁵ To conclude the section on the synthesis of 3,4'-bipyridines, a number of reactions leading

⁶⁴¹ R. H. Wiley and J. S. Ridgway, *J. Org. Chem.* **26**, 595 (1961).

⁶⁴² O. S. Otroshchenko, A. A. Ziyaev, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.*, 365 (1969).

⁶⁴³ A. S. Alvarez-Insua, M. Lora-Tamayo, and J. L. Soto, *J. Heterocycl. Chem.* **7**, 1305 (1970).

⁶⁴⁴ P. Nantka-Namirski and R. Balicki, *Acta Pol. Pharm.* **31**, 271 (1974).

⁶⁴⁵ M. A. Cabrerizo and J. L. Soto, *An. Quim.* **70**, 951 (1974).

⁶⁴⁶ M. Mallet and G. Queguiner, *Tetrahedron* **35**, 1625 (1979).

⁶⁴⁷ H. Strzelecka and M. Simalty, *Bull. Soc. Chim. Fr.*, 832 (1968).

⁶⁴⁸ H. Strzelecka and M. Simalty, *Bull. Soc. Chim. Fr.*, 4122 (1968).

to 3,4'-bipyridinones are worthy of mention. Cyclization of α -nicotinyl-propionitrile with phenylacetone, using polyphosphoric acid, affords 3',6'-dimethyl-5'-phenyl-3,4'-bipyridin-2'-one.⁶⁴⁹ In reactions analogous to those referred to in Sections III.B, C, and D, several condensations involving cyanoacetamide give rise to cyano-substituted 3,4'-bipyridinones such as **66** and related compounds.^{588,611,650-660}

F. 4,4'-BIPYRIDINE

Several of the methods of synthesis of 2,2'-bipyridines have their counterpart in the preparation of 4,4'-bipyridine. The Ullmann reaction has been used to prepare 4,4'-bipyridine. Thus 4-halogenated pyridines afford 4,4'-bipyridine.^{414,425} Dehalogenation and dimerization of 4-bromopyridine may be accomplished too with hydrazine and alkali at 65°C in the presence of a palladium catalyst,⁶⁶¹ whereas 4-chloropyridine is converted to 4,4'-bipyridine in 46% yield by reaction with alkaline sodium formate in the presence of palladium on charcoal and a surfactant.⁴²⁴ Several extensions of the Ullmann reaction have recently been reported, especially for the synthesis of substituted 4,4'-bipyridines. Thus 4-iodo-2-methylpyridine gives 2,2'-dimethyl-4,4'-bipyridine,⁶⁶² 3-nitro-4-chloropyridine affords 3,3'-dinitro-4,4'-bipyridine,^{442,663} 4-bromo- or 4-iodotetrafluoropyridine gives octafluoro-4,4'-bipyridine,^{664,665} and 4-iodo- or 4-bromotetrachloropyridine gives octachloro-4,4'-bipyridine.^{625,666} Related syntheses have been de-

⁶⁴⁹ C. R. Hauser and C. J. Eby, *J. Am. Chem. Soc.* **79**, 728 (1957).

⁶⁵⁰ P. Nantka-Namirski and R. Balicki, *Acta Pol. Pharm.* **29**, 131 (1972).

⁶⁵¹ P. Nantka-Namirski and R. Balicki, *Acta Pol. Pharm.* **29**, 545 (1972).

⁶⁵² P. Nantka-Namirski and R. Balicki, Polish Patent 72,750 (1974) [*CA* **85**, 21120 (1976)].

⁶⁵³ G. Y. Leshner and C. J. Opalka, U. S. Patent 4,107,315 (1978) [*CA* **90**, 103844 (1979)].

⁶⁵⁴ P. Nantka-Namirski and L. Kaczmarek, *Pol. J. Pharmacol. Pharm.* **30**, 707 (1978).

⁶⁵⁵ K. O. Gelotte and C. J. Opalka, U.S. Patent 4,264,609 (1981) [*CA* **95**, 62012 (1981)].

⁶⁵⁶ G. Y. Leshner and C. J. Opalka, Canadian Patent 1,103,254 (1981) [*CA* **95**, 187078 (1981)].

⁶⁵⁷ F. W. Gubitz, *J. Labelled Compd. Radiopharm.* **18**, 755 (1981).

⁶⁵⁸ G. Y. Leshner, R. E. Philion, D. F. Page, and C. J. Opalka, French Patent 2,470,124 (1981) [*CA* **96**, 6594 (1982)].

⁶⁵⁹ G. Y. Leshner and C. J. Opalka, Canadian Patent 1,103,253 (1981) [*CA* **96**, 52183 (1982)].

⁶⁶⁰ K. O. Gelotte and E. D. Parady, French Patent 2,476,648 (1981) [*CA* **96**, 104107 (1982)].

⁶⁶¹ G. J. Moore, German Patent 2,230,562 (1973) [*CA* **79**, 42351 (1973)].

⁶⁶² E. Proffitt and H. Richter, *J. Prakt. Chem.* **9**, 164 (1959).

⁶⁶³ S. Kanoktanaporn and J. A. H. MacBride, *J. C. S. Perkin I*, 1126 (1978).

⁶⁶⁴ R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 5040 (1965).

⁶⁶⁵ R. E. Banks, R. N. Haszeldine, E. Phillips, and I. M. Young, *J. Chem. Soc. C*, 2091 (1967).

⁶⁶⁶ I. Collins, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc. C*, 167 (1971).

scribed.^{665,667,668} Octafluoro-4,4'-bipyridine is also formed from pentafluoropyridine in the presence of trimethyltinlithium⁶⁶⁹ and triethyl phosphite and related species.^{670,671} Related organolithium reactions have been applied to give polychloro-4,4'-bipyridines.^{672,673} Pentafluoropyridine also gives octafluoro-4,4'-bipyridine on electrochemical reduction, but pentachloropyridine is not similarly reduced.^{388,674} 4-Bromo-2,6-dimethylpyridine with lead acetate gives a small amount of 2,2',6,6'-tetramethyl-4,4'-bipyridine.⁶⁷⁵ Grignard-type reagents from 4-halogenated pyridines can also be converted to 4,4'-bipyridine,^{415,425} and several other examples particularly leading to octahalogenated 4,4'-bipyridines have been reported.^{625,664,665,672,676}

As in the case of 2,2'-bipyridine, the most important synthetic routes to 4,4'-bipyridine use pyridine as starting material. One method of synthesizing 4,4'-bipyridine from pyridine was discovered by Dimroth in 1921. If pyridine in acetic anhydride is treated with zinc dust, 1,1'-diacetyl-1,1',4,4'-tetrahydro-4,4'-bipyridine is formed. This compound is readily oxidized and hydrolyzed by moist air to 4,4'-bipyridine.⁶⁷⁷ Various oxidizing agents assist in the conversion to 4,4'-bipyridine. By-products from the reaction include 1,1'-diacetyl-1,1'-dihydro-4,4'-bipyridine.⁶⁷⁸ This method of synthesizing 4,4'-bipyridine has frequently been used.^{679,680} The reduction of pyridine in acetic anhydride by catalytic hydrogenation instead of by zinc dust is less satisfactory because of the formation of other reduction products.⁶⁸¹ Several variations and improvements in the Dimroth reaction have subsequently

⁶⁶⁷ R. E. Banks, R. N. Haszeldine, and E. Phillips, *J. Fluorine Chem.* **9**, 243 (1977).

⁶⁶⁸ E. J. Soloski, W. E. Ward, and C. Tamborski, *J. Fluorine Chem.* **2**, 361 (1973).

⁶⁶⁹ M. Green, A. Taunton-Rigby, and F. G. A. Stone, *J. Chem. Soc. A*, 2762 (1968).

⁶⁷⁰ L. N. Markovskii, G. G. Furin, Y. G. Shermolovich, and G. G. Yakobson, *Zh. Obshch. Khim.* **49**, 531 (1979).

⁶⁷¹ L. N. Markovskii, G. G. Furin, Y. G. Shermolovich, O. N. Tychkina, and G. G. Yakobson, *Zh. Obshch. Khim.* **49**, 710 (1979).

⁶⁷² S. S. Dua and H. Gilman, *J. Organomet. Chem.* **12**, 299 (1968).

⁶⁷³ N. J. Foulgar and B. J. Wakefield, *J. Organomet. Chem.* **69**, 161 (1974).

⁶⁷⁴ R. D. Chambers, D. T. Clark, C. R. Sargent, and F. G. Drakesmith, *Tetrahedron Lett.*, 1917 (1979).

⁶⁷⁵ Y. Tamaru, Y. Yamada, T. Arimoto, and Z. Yoshida, *Chem. Lett.*, 975 (1978).

⁶⁷⁶ Y. N. Ivanshchenko, S. D. Moshchitskii, and A. K. Eliseeva, *Khim. Geterotsikl. Soedin.*, 58 (1970).

⁶⁷⁷ O. Dimroth and R. Heene, *Ber. Dtsch. Chem. Ges. B* **54**, 2934 (1921).

⁶⁷⁸ O. Dimroth and F. Frister, *Ber. Dtsch. Chem. Ges. B* **55**, 1223 (1922).

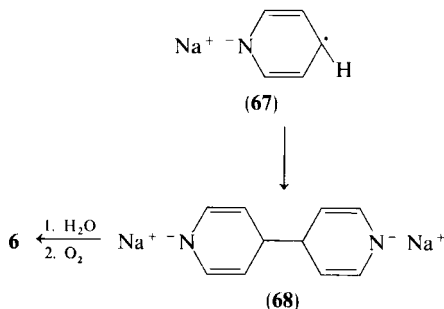
⁶⁷⁹ L. Michaelis and E. S. Hill, *J. Am. Chem. Soc.* **55**, 1484 (1933).

⁶⁸⁰ P. Szarvas, J. Emri, B. Gyori, Z. Nagy, K. Punkosti, J. Bonczor, S. Arany, and B. Gyori, Hungarian Patent 157,374 (1970) [*CA* **73**, 66444 (1970)].

⁶⁸¹ J. F. Arens and J. P. Wibaut, *Recl. Trav. Chim. Pays-Bas* **61**, 452 (1942).

been reported.⁶⁸²⁻⁶⁸⁸ Under favorable conditions, yields of 4,4'-bipyridine in excess of 50% may be obtained.

The most important synthesis of 4,4'-bipyridine involves the reaction of sodium on pyridine. This reaction was discovered as long ago as 1870,⁶⁸⁹ although the product was not deduced to be 4,4'-bipyridine until later.⁹⁴ 4,4'-Bipyridine is the predominant isomer formed,⁶²⁶ although varying amounts of other isomeric bipyridines, especially 2,2'-bipyridine and 2,4'-bipyridine, may be formed, depending on the reaction conditions. The reaction involves formation of the sodium derivative of pyridine, which is formulated as the radical **67**. It then couples predominantly in the 4 positions to afford **68**, which with water hydrolyzes to 1,1',4,4'-tetrahydro-4,4'-bipyridine. Facile oxidation then gives 4,4'-bipyridine.⁶⁹⁰ If the reaction is carried out at the temperature of boiling pyridine (115°C) instead of at lower temperatures, the proportion of bipyridines other than 4,4'-bipyridine increases, and some terpyridines may be formed as well.^{626,691-696} Oxidants



⁶⁸² E. Weitz, A. Roth, and A. Nelken, *Justus Liebigs Ann. Chem.* **425**, 161 (1921).

⁶⁸³ D. A. Van Dorp and J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **66**, 189 (1947).

⁶⁸⁴ O. Dimroth and F. Frister, *Ber. Dtsch. Chem. Ges. B* **55**, 3693 (1922).

⁶⁸⁵ A. E. Arbuzov, *Bull. Acad. Sci. URSS, Cl. Sci. Chim.*, 451 (1945).

⁶⁸⁶ J. Bonczos, P. Szarvas, E. Gyori, J. Emri, S. Arany, K. Punkosty, and Z. Nagy, German Patent 1,926,535 (1969) [*CA* **72**, 55271 (1970)].

⁶⁸⁷ F. Lindwurm and J. Tomasz, Hungarian Patent 2,387 (1971) [*CA* **75**, 129672 (1971)].

⁶⁸⁸ A. Takeuchi, K. Ito, and M. Sekiya, *Chem. Pharm. Bull.* **25**, 1363 (1977).

⁶⁸⁹ T. Anderson, *Justus Liebigs Ann. Chem.* **154**, 270 (1870).

⁶⁹⁰ B. Emmert, *Ber. Dtsch. Chem. Ges.* **50**, 31 (1917).

⁶⁹¹ W. Schulenburg, German Patent 588,041 (1933) [*CA* **28**, 1486 (1934)].

⁶⁹² R. H. Linnell and A. B. Zahlan, U.S. Patent 2,773,066 (1956) [*CA* **51**, 5845 (1957)].

⁶⁹³ Imperial Chemical Industries Ltd., Belgian Patent 617,852 (1962) [*CA* **60**, 2907 (1964)].

⁶⁹⁴ Imperial Chemical Industries Ltd., Belgian Patent 629,552 (1963) [*CA* **60**, 14482 (1964)].

⁶⁹⁵ K. Holowiecki, J. Horak, and M. Rozmarynowicz, *Lodz. Tow. Nauk., Pr. Wyd.* **3** **9**, 177 (1964) [*CA* **62**, 9100 (1965)].

⁶⁹⁶ R. Vilceanu, E. Dumitrescu, I. Neamtii, M. Knejev, and F. Neamtii, Romanian Patent 57,258 (1974) [*CA* **83**, 206108 (1975)].

have sometimes been added to assist the air oxidation of the tetrahydro-bipyridine to 4,4'-bipyridine.^{697,698}

The best yields of 4,4'-bipyridine are obtained if pyridine is allowed to react with sodium in liquid ammonia at about -40°C in the presence of a solvent, such as 1,2-dimethoxyethane or dimethylformamide, and the mixture is oxidized by air. In this way yields of 4,4'-bipyridine as high as 84%, largely free of other isomeric bipyridines, can be obtained,^{699,700} and this is the method used for the manufacture of 4,4'-bipyridine on the scale necessary for the synthesis of the herbicide paraquat⁴⁶⁷ (see Section IV,D). At higher temperatures (e.g., 130°C) the reaction of the sodium derivative of pyridine with anhydrous ammonia⁷⁰¹ or of pyridine with sodamide under Chichibabin conditions gives mainly aminopyridines, although some 4,4'-bipyridine and other bipyridines are also formed.^{93,702,703} A considerable amount of work has also been reported on the use of magnesium-sodium mixtures in reaction with pyridine, but the yields of 4,4'-bipyridine are not as high as in the sodium-liquid ammonia process.^{467,704} Aluminum can be used instead of sodium or magnesium, but here also the yields of 4,4'-bipyridine are usually not as high.^{694,705} The mechanism of the reaction of alkali metals on pyridine has been the subject of some reports.^{308,706} A 1975 patent, describes the reaction of pyridine with sodium in $(\text{Me}_2\text{N})_3\text{PO}$ at low temperatures, followed by oxidation of the mixture by air, which also gives a good yield of 4,4'-bipyridine.⁷⁰⁷ 2,2'-Bipyridines contaminating 4,4'-bipyridine may be removed as their metal chelates,^{708,709} whereas 4,4'-bipyridine can be separated from 2,4'-bipyridine as its relatively insoluble dihydrate.⁷¹⁰ Symmetrically substituted 4,4'-bipyridines are likewise obtainable from the reaction of substituted

⁶⁹⁷ R. Setton, *C. R. Hebd. Seances Acad. Sci.* **244**, 1205 (1957).

⁶⁹⁸ Imperial Chemical Industries Ltd., French Patent 1,341,585 (1963) [CA **60**, 14482 (1964)].

⁶⁹⁹ Imperial Chemical Industries Ltd., French Patent 1,380,806 (1964) [CA **62**, 10417 (1965)].

⁷⁰⁰ Imperial Chemical Industries Ltd., Netherlands Patent 6,603,415 (1966) [CA **66**, 28674 (1967)].

⁷⁰¹ E. Schering, German Patent 358,397 (1922) [CA **17**, 2118 (1923)].

⁷⁰² M. T. Leffler, *Org. React. (N.Y.)* **1**, 91-104 (1942).

⁷⁰³ T. Vajda and K. Kovacs, *Recl. Trav. Chim. Pays-Bas* **80**, 47 (1961).

⁷⁰⁴ For example, Imperial Chemical Industries Ltd., Belgian Patent 617,748 (1962) [CA **58**, 13922 (1963)].

⁷⁰⁵ Imperial Chemical Industries Ltd., Belgian Patent 622,407 (1963) [CA **59**, 9999 (1963)].

⁷⁰⁶ A. A. Ziyaev, O. S. Otroshchenko, V. B. Leont'ev, and A. S. Sadykov, *Zh. Org. Khim.* **1**, 1884 (1965).

⁷⁰⁷ R. Vilceanu, I. Neamtii, M. Knejev, and F. Neamtii, Romanian Patent 58,183 (1975) [CA **85**, 142987 (1976)].

⁷⁰⁸ G. I. Mikhailov and L. I. Mizrakh, U.S.S.R. Patent 123,946 (1959) [CA **54**, 9963 (1960)].

⁷⁰⁹ Imperial Chemical Industries Ltd., Netherlands Patent 6,401,239 (1964) [CA **62**, 4011 (1965)].

⁷¹⁰ Imperial Chemical Industries Ltd., Belgian Patent 628,926 (1963) [CA **61**, 6995 (1964)].

pyridines with sodium. Thus 2-picoline affords 2,2'-dimethyl-4,4'-bipyridine,^{693,699,711,712} 3-picoline gives 3,3'-dimethyl-4,4'-bipyridine,⁷¹³ 2,6-dimethylpyridine gives 2,2',6,6'-tetramethyl-4,4'-bipyridine,^{693,714} and anabasine and *N*-methylanabasine afford 3,3'-dipiperidyl-4,4'-bipyridines.^{715,716} Methyl nicotinate gives 4,4'-bipyridine-3,3'-dicarboxylic acid,⁷¹⁷ whereas 3-fluoropyridine with potassium amide in liquid ammonia affords 3,3'-difluoro-4,4'-bipyridine as one of the products of the reaction.⁵⁹⁴ Some 3-fluoro-4,4'-bipyridine was also formed. Pyridine 1-oxide hydrochloride also reacts with sodium in liquid ammonia at -40°C to afford 4,4'-bipyridine,⁷¹⁸ and related reactions have subsequently been observed.⁷¹⁹ Reaction of pyridine 1-oxide with benzophenone lithium ketyls also gave some 4,4'-bipyridine as a by-product.^{720,721}

As in the synthesis of other bipyridines, several routes to 4,4'-bipyridine have been devised where one of the pyridine rings is built up from simpler components. For example, a dimer of acrolein reacts with ammonia and methanol in the presence of boron phosphate catalyst at 350°C to give a mixture of products including 4,4'-bipyridine (3.4% yield),⁵⁹⁷ and in a reaction akin to ones referred to with other bipyridines, 4-vinylpyridine reacts with substituted oxazoles in the presence of acid to give substituted 4,4'-bipyridines.^{602,603} Condensation of isonicotinaldehyde with acetaldehyde and ammonia at high temperatures in the presence of a catalyst also affords some 4,4'-bipyridine, and related processes give similar results,⁷²² whereas pyran derivatives can be converted to 4,4'-bipyridine (56% conversion), for example, by reaction with ammonia and air at 350°C with a nickel-alumina catalyst.^{723,724} Likewise, 2,6-diphenyl-4-(4-pyridyl)pyrylium salts afford 2,6-

⁷¹¹ F. B. Ahrens, *Ber. Dtsch. Chem. Ges.* **21**, 2929 (1888).

⁷¹² A. Heuser and C. Stoeck, *J. Prakt. Chem.* **42**, 429 (1889).

⁷¹³ C. Stoeck and M. Wagner, *J. Prakt. Chem.* **48**, 1 (1893).

⁷¹⁴ F. Huth, *Ber. Dtsch. Chem. Ges.* **31**, 2280 (1898).

⁷¹⁵ A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, and G. A. Tolkacheva, *Khim. Geterotsikl. Soedin.*, 364 (1969).

⁷¹⁶ A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, G. A. Tolkacheva, and T. A. Khodzhaeva, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **419**, 200 (1972) [*CA* **79**, 31804 (1973)].

⁷¹⁷ A. A. Ziyaev, K. D. Khalilova, O. S. Otroshchenko, G. A. Tolkacheva, and A. S. Sadykov, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **462**, 13 (1974) [*CA* **84**, 30823 (1976)].

⁷¹⁸ M. Ishikawa and K. Tokuyama, *Annu. Rep. Shionogi Res. Lab.*, 37 (1953) [*CA* **50**, 14752 (1956)].

⁷¹⁹ M. Itoh and T. Okamoto, *Chem. Pharm. Bull.* **15**, 435 (1967).

⁷²⁰ A. S. Kurbatova, Y. V. Kurbatov, and D. A. Niyazova, *Khim. Geterotsikl. Soedin.*, 655 (1979).

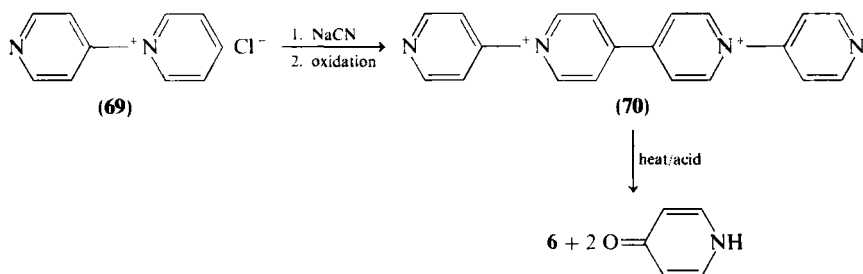
⁷²¹ A. S. Kurbatova, Y. V. Kurbatov, and N. M. Dmitrieva, *Zh. Org. Khim.* **16**, 648 (1980).

⁷²² I. Lazdins and A. Avots, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 427 (1974) [*CA* **81**, 169409 (1974)].

⁷²³ R. D. Bowden, German Patent 1,913,150 (1969) [*CA* **72**, 43449 (1970)].

⁷²⁴ G. J. Moore and M. T. Richardson, British Patent 1,424,679 (1976) [*CA* **84**, 180064 (1976)].

diphenyl-4,4'-bipyridine on reaction with aqueous ammonia in ethanol.⁷²⁵ 3-(4-Pyridyl)-1,5-pentandiol reacting with ammonia at 350°C under pressure gives an 81% yield of 4,4'-bipyridine, using palladium-charcoal as the dehydrogenating catalyst.⁷²⁶ Several related derivatives such as 4-(4-piperidyl)pyridine and 4-(4-pyridyl)tetrahydropyran are likewise converted to 4,4'-bipyridine.^{562,727,728} An interesting synthesis of 4,4'-bipyridine involves dimerization of 1-(4-pyridyl)pyridinium chloride (**69**) with sodium cyanide to give 1,1'-di(4-pyridyl)-1,1'-dihydro-4,4'-bipyridine, which is oxidized in 74% yield to the diquaternary salt **70**. The salt on heating with



acid affords 4,4'-bipyridine and 4-pyridone.⁷²⁹ A number of minor routes to 4,4'-bipyridine are worthy of note. It is formed by dehydrogenation of 4,4'-bipiperidine,⁵⁹⁵ by treatment of 2,2'-dimethyl-4,4'-bipyridine with steam and a nickel catalyst,⁷³⁰ by γ irradiation of pyridine,⁵²⁷ and as a by-product of various electrolytic reactions conducted in pyridine.⁷³¹⁻⁷³³ 2,2'-Dimethyl-4,4'-bipyridine is among the products obtained by γ irradiation of 2-picoline⁷³⁴ and is also formed by electrolysis of 2-picoline in liquid ammonia.⁷³⁵

⁷²⁵ A. R. Katritzky, J. Adamson, E. M. Elisseou, G. Musamarra, R. C. Patel, K. Sakizadeh, and W. K. Yeung, *J. C. S. Perkin II*, 1041 (1982).

⁷²⁶ R. D. Bowden, German Patent 2,033,958 (1971) [*CA* **74**, 64208 (1971)].

⁷²⁷ R. D. Bowden, German Patent 2,022,928 (1970) [*CA* **74**, 42285 (1971)]; British Patent 1,268,195 (1972) [*CA* **76**, 126789 (1972)]; German Patent 1,913,732 (1970) [*CA* **72**, 132535 (1970)]; British Patent 1,268,194 (1972) [*CA* **76**, 126790 (1972)]; British Patent 1,268,191 (1972) [*CA* **76**, 126791 (1972)]; British Patent 1,268,193 (1972) [*CA* **76**, 153617 (1972)].

⁷²⁸ R. D. Bowden and T. Seaton, British Patent 1,324,644 (1973) [*CA* **79**, 126323 (1973)].

⁷²⁹ R. H. Reuss and L. J. Winters, *J. Org. Chem.* **38**, 3993 (1973).

⁷³⁰ G. J. Moore, British Patent 1,381,038 (1975) [*CA* **83**, 9811 (1975)].

⁷³¹ M. D. Rausch, F. D. Popp, W. E. McEwen, and J. Kleinberg, *J. Org. Chem.* **21**, 212 (1956).

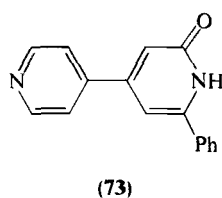
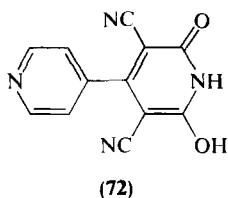
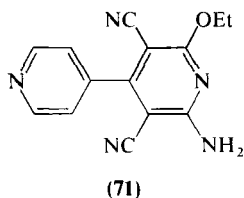
⁷³² T. T. Tsai, W. E. McEwen, and J. Kleinberg, *J. Org. Chem.* **25**, 1186 (1960).

⁷³³ T. T. Tsai, W. E. McEwen, and J. Kleinberg, *J. Org. Chem.* **26**, 318 (1961).

⁷³⁴ V. E. Riskovets, V. V. Saraeva, and S. V. Zatonskii, *Vestn. Mosk. Univ., Ser. 2: Khim.* **17**, 493 (1976) [*CA* **86**, 63424 (1977)].

⁷³⁵ K. Junghans, German Patent 2,811,803 (1979) [*CA* **92**, 6421 (1980)].

To complete the section on the synthesis of 4,4'-bipyridines, we summarize the methods reported for the preparation of some substituted 4,4'-bipyridines and 4,4'-bipyridinones. These methods are closely analogous to syntheses already discussed for some of the isomeric bipyridines. Thus the Hantzsch reaction using pyridine-4-aldehyde, ethyl acetoacetate, and ammonia gives 3,5-di(ethoxycarbonyl)-1,4-dihydro-2,6-dimethyl-4,4'-bipyridine, which after oxidation, followed by hydrolysis and decarboxylation, afforded 2,6-dimethyl-4,4'-bipyridine.^{91,736} Several related condensations have been reported.⁵⁹⁸⁻⁶⁰⁰ Similarly, pyridine-4-aldehyde and excess acetophenone gave 1,5-diphenyl-3-(4-pyridyl)pentane-1,5-dione, which with ammonium acetate afforded 2,6-diphenyl-4,4'-bipyridine.⁷³⁷ Alternatively, 1-phenyl-3-(4-pyridyl)prop-2-enone, *N*-phenacylpyridinium bromide, and ammonium acetate gave the same diphenyl-4,4'-bipyridine,^{737,738} and extensions of this synthesis have been described.^{546,607,739} Condensation of pyridine-4-aldehyde with malononitrile in the presence of an alcohol and alkaline catalyst produced compounds such as **71**,⁶⁴⁴ whereas condensations of pyridine-4-aldehyde with cyanoacetamide and ammonia gave structure **72**.⁶⁵⁰⁻⁶⁵² In a synthesis analogous to that described in Section III.B, a Michael condensation involving 1-(carbamoylmethyl)pyridinium chloride and 1-phenyl-3-(4-pyridyl)prop-2-enone affords the 4,4'-bipyridinone **73**.⁵⁴⁵



IV. General Reactions

A. REDUCTION

2,2'-Bipyridine is fully reduced to 2,2'-bipiperidine by sodium in boiling alcohols,^{84,740,741} by catalytic hydrogenation,⁷⁴²⁻⁷⁴⁵ and by electrochemical means.^{746,747} Sometimes two forms of 2,2'-bipiperidine have been isolated,

⁷³⁶ W. Treibs and J. Beger, *Justus Liebigs Ann. Chem.* **652**, 192 (1962).

⁷³⁷ J. E. Downes, *J. Chem. Soc. C*, 1491 (1967).

⁷³⁸ S. Hunig and G. Ruider, *Tetrahedron Lett.*, 773 (1968).

⁷³⁹ S. Hunig, B. J. Garner, G. Ruider, and W. Schenk, *Justus Liebigs Ann. Chem.* 1036 (1973).

⁷⁴⁰ P. Krumholz, *J. Am. Chem. Soc.* **75**, 2163 (1953).

⁷⁴¹ Y. N. Forostyan, E. I. Efimova, and I. I. Soroka, *Zh. Org. Khim.* **7**, 2198 (1971).

⁷⁴² C. R. Smith, *J. Am. Chem. Soc.* **50**, 1936 (1928).

which are considered to be erythro and threo isomers.^{741,744,747} 1,2,3,4,5,6-Hexahydro-2,2'-bipyridine can be obtained by the reduction of 2,2'-bipyridine by tin and hydrochloric acid,^{743,748} by aluminum in aqueous alkali,⁷⁴¹ by controlled catalytic hydrogenation,⁷⁴⁹ and under certain conditions on electrochemical reduction. In the last method some dihydro and tetrahydro-2,2'-bipyridines may also be formed.^{746,750,751} 2,2'-Bipyridine is reduced to 1,4-dihydro-2,2'-bipyridine by bisdihydropyridyl metal complexes,²⁷⁰ to 1,2- and 1,4-dihydro-2,2'-bipyridines by lithium aluminum hydride,²⁹⁸ and to its radical anion by alkali metals, and by irradiation and related reactions.^{298,752-752c} Subsequent hydrolysis of the radical anion can lead to 3,4,5,6-tetrahydro-2,2'-bipyridine and 1,2,3,4,5,6-hexahydro-2,2'-bipyridine⁷⁵³ or dihydrobipyridines.²⁹⁸ Radical anions of dimethyl-2,2'-bipyridines⁷⁵⁴ and 2,2':6',2''-terpyridine⁷⁵⁵ have also been studied. The one-electron reduction of 2,2'-bipyridine in aqueous solution by pulse radiolysis has also been investigated.^{756,757}

Similarly 2,3'-bipyridine is reduced to 2,3'-bipiperidine by sodium in alcohol⁷⁵⁸ or by catalytic hydrogenation.^{553,742} Two forms of 2,3'-bipiperidine have been reported to be obtained in this way.⁵⁵³ Partial hydrogenation of 2,3'-bipyridine, for example, by tin and hydrochloric acid affords 1',2',3',4',5',6'-hexahydro-2,3'-bipyridine, an isomer of anabasine (12:

⁷⁴³ M. T. Beck and M. Halmos, *Nature (London)* **191**, 1090 (1961).

⁷⁴⁴ D. C. Allport, *SCI Monogr.* **25**, 143 (1967).

⁷⁴⁵ G. D. Khandelwal, G. A. Swan, and R. B. Roy, *J. C. S. Perkin I*, 891 (1974).

⁷⁴⁶ Y. N. Forostyan, A. P. Oleinik, and V. M. Artemova, *Elektrokhimiya* **7**, 715 (1971).

⁷⁴⁷ V. M. Artemova, Y. N. Forostyan, V. G. Govorukha, and E. I. Forostyan, *Elektrokhimiya* **12**, 1816 (1976).

⁷⁴⁸ C. R. Smith, *J. Am. Chem. Soc.* **53**, 277 (1931).

⁷⁴⁹ P. N. Rylander and D. R. Steele, U.S. Patent 3,387,048 (1968) [*CA* **69**, 26968 (1968)].

⁷⁵⁰ H. Erhard and W. Jaenicke, *J. Electroanal. Chem. Interfacial Electrochem.* **81**, 79 (1977).

⁷⁵¹ H. Erhard and W. Jaenicke, *J. Electroanal. Chem. Interfacial Electrochem.* **81**, 89 (1977).

⁷⁵² J. Wendenburg and H. Moeckel, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **23B**, 1171 (1968); E. Koenig and S. Kremer, *Chem. Phys. Lett.* **5**, 87 (1970).

^{752a} C. David, P. Janssen, and G. Geuskens, *Spectrochim. Acta, Part B* **27B**, 367 (1971).

^{752b} T. Iizuka, *Chem. Lett.*, 891 (1973).

^{752c} K. Gustav, *Z. Phys. Chem. (Leipzig)* **257**, 28 (1976).

⁷⁵³ R. Weil and N. Collignon, *Bull. Soc. Chim. Fr.*, 258 (1974).

⁷⁵⁴ Y. Torii, T. Yazaki, Y. Kaizu, S. Murasato, and H. Kobayashi, *Bull. Chem. Soc. Jpn.* **42**, 2264 (1969).

⁷⁵⁵ K. Nakamura, *Bull. Chem. Soc. Jpn.* **45**, 1943 (1972).

⁷⁵⁶ M. Z. Hoffman, M. G. Simic, Q. G. Mulazzani, S. Emmi, P. G. Fuochi, and M. Venturi, *Radiat. Phys. Chem.* **12**, 111 (1978).

⁷⁵⁷ Q. G. Mulazzani, S. Emmi, P. G. Fuochi, M. Venturi, M. Z. Hoffman, and M. G. Simic, *J. Phys. Chem.* **83**, 1582 (1979).

⁷⁵⁸ F. Blau, *Monatsh. Chem.* **13**, 330 (1892).

R = H).^{558,748,759} A substituted 2,3'-bipyridine likewise is preferentially reduced in the β -pyridyl ring.⁵⁷¹ 2,3'-Bipyridine is reduced to the 1',4'-dihydro derivative by bisdihydropyridyl metal complexes,²⁷⁰ and 2,4'-bipyridine is likewise reduced to its 1',4'-dihydro derivative.²⁷⁰

3,3'-Bipyridine is catalytically hydrogenated to 3,3'-bipiperidine,⁷⁴² and the reduction may also be accomplished electrochemically. Erythro and threo forms of 3,3'-bipiperidine are produced by the latter method.^{747,760} 3,3'-Bipyridine is reduced with difficulty by means of tin and hydrochloric acid or sodium and alcohol. Some 1,2,3,4,5,6-hexahydro-3,3'-bipyridine (also known as nicotidine) is produced,^{97,748} but several other partly reduced 3,3'-bipyridines are obtained as well.⁷⁶¹ 3,3'-Bipyridine is reported to give a radical anion in tetrahydrofuran on reduction by sodium.⁷⁶² Although there is some doubt about the authenticity of the starting material (see Section III,E), 3,4'-bipyridine is reported to be fully reduced to 3,4'-bipiperidine by catalytic hydrogenation⁷⁴² and to 1',2',3',4',5',6'-hexahydro-3,4'-bipyridine by tin and hydrochloric acid.⁷⁴⁸

4,4'-Bipyridine is likewise reduced to 4,4'-bipiperidine by sodium and amyl alcohol⁷⁶³ and by catalytic hydrogenation.^{742,744,764,765} 2,2'-Dimethyl-4,4'-bipyridine is reduced to 2,2'-dimethyl-4,4'-bipiperidine.⁷¹³ Electrochemical reduction of 4,4'-bipyridine affords 4,4'-bipiperidine and some partly reduced 4,4'-bipyridines.^{746,747} Further work on the electroreduction of 4,4'-bipyridine has been reported.⁷⁶⁶ Reduction of 4,4'-bipyridine by tin and hydrochloric acid^{94,748} or by controlled catalytic hydrogenation^{767,768} gives 1,2,3,4,5,6-hexahydro-4,4'-bipyridine. 4,4'-Bipyridine is reduced to its 1,4-dihydro derivative by bisdihydropyridyl metal complexes²⁷⁰ and to its radical anion by alkali metals and related processes.^{306,752b,769} The ionization constant of the radical anion has been determined.⁷⁷⁰

⁷⁵⁹ G. Menschikoff and A. Grigorovitch, *Ber. Dtsch. Chem. Ges. B* **69**, 496 (1936).

⁷⁶⁰ Y. N. Forostyan, E. I. Lyushina, V. M. Artemova, and V. G. Govorukha, *Elektrokhimiya* **12**, 73 (1976).

⁷⁶¹ Y. N. Forostyan and E. I. Efimova, *Zh. Obshch. Khim.* **39**, 2122 (1969).

⁷⁶² N. Zengin, G. Bingol, and B. Ozbay, *Commun. Fac. Sci. Univ. Ankara, Ser. A* **16**, 19 (1967) [*CA* **68**, 109818 (1968)].

⁷⁶³ F. B. Ahrens, *Ber. Dtsch. Chem. Ges.* **24**, 1478 (1891).

⁷⁶⁴ F. F. Blicke and E. B. Hotelling, *J. Am. Chem. Soc.* **76**, 5099 (1954).

⁷⁶⁵ A. P. Phillips and J. Mentha, *J. Am. Chem. Soc.* **77**, 6393 (1955).

⁷⁶⁶ N. K. Kiva, V. M. Artemova, L. V. Dulenko, and F. I. Kogan, *Tezisy Dokl.—Vses. Soveshch. Polyarogr.*, 7th, 1978, 66 (1978) [*CA* **92**, 205998 (1980)].

⁷⁶⁷ D. C. Allport, British Patent 1,130,551 (1968) [*CA* **70**, 28832 (1969)].

⁷⁶⁸ D. C. Allport, British Patent 1,129,511 (1968) [*CA* **70**, 28833 (1969)].

⁷⁶⁹ J. W. Dodd, F. J. Hopton, and N. S. Hush, *Proc. Chem. Soc., London*, 61 (1962).

⁷⁷⁰ P. S. Rao and E. Hayon, *Anal. Chem.* **48**, 564 (1976).

B. OXIDATION

2,2'-Bipyridine is oxidized by hot permanganate to picolinic acid.⁸⁴ 2,2':6',2''-Terpyridine is also oxidized to picolinic acid,⁷⁷¹ whereas 4,4'-dichloro-2,2'-bipyridine gives 4-chloropicolinic acid.⁷⁷² Interestingly, 2,2'-bipyridine is oxidized to its radical cation by loss of an electron at low temperatures on γ irradiation in *sec*-butyl chloride.^{752a} The alkaloid isonicotine, which was subsequently shown to be identical with 2,3'-bipyridine, is oxidized to nicotinic acid,^{74,75} and 5-hydroxy-2,3'-bipyridine is likewise oxidized by potassium permanganate to nicotinic acid,⁵⁶⁴ whereas the terpyridine nicotelline (**10**) affords 3,4'-bipyridine-2'-carboxylic acid, pyridine-2,4-dicarboxylic acid, and nicotinic acid.¹⁶ 2,4'-Bipyridine is oxidized by permanganate to picolinic acid and isonicotinic acid,^{89,90,595} and substituted 2,4'-bipyridines are oxidized in the same way.⁸⁹ 3,3'-Bipyridine is oxidized to nicotinic acid,⁹⁷ and 3,3'-bipyridine-5-carboxylic acid likewise affords pyridine-3,5-dicarboxylic acid.⁷⁷³ As expected, 3,4'-bipyridine is oxidized to nicotinic and isonicotinic acids,^{89,626} and substituted derivatives behave similarly.⁸⁹ On oxidation by permanganate, 4,4'-bipyridine affords isonicotinic acid.^{94,595} Substituted 4,4'-bipyridines are oxidized in a similar way.^{774,775}

C. SUBSTITUTION REACTIONS

The electron-deficient bipyridines require drastic conditions for electrophilic substitution, which would be expected to take place at positions β to the nitrogen atoms. Nucleophilic substitution would be expected to proceed at sites α and γ to the nitrogen atoms.

Vapor-phase chlorination of 2,2'-bipyridine at 555°C gives the fully chlorinated octachloro-2,2'-bipyridine in over 90% yield.⁷⁷⁶ Reaction of 2,2'-bipyridine at 300°C with phosphorus pentachloride also affords octachloro-2,2'-bipyridine.⁷⁷⁷ At lower temperatures (200–400°C) the vapor phase

⁷⁷¹ G. Morgan and F. H. Burstall, *J. Chem. Soc.*, 1649 (1937).

⁷⁷² J. Haginiwa, *J. Pharm. Soc. Jpn.* **75**, 731, 733 (1955).

⁷⁷³ O. S. Otroshchenko, Y. V. Kurbatov, and A. S. Sadykov, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **286**, 88 (1966) [*CA* **67**, 99969 (1967)].

⁷⁷⁴ O. S. Otroshchenko, A. S. Sadykov, and A. A. Ziyaev, *Zh. Obshch. Khim.* **31**, 678 (1961).

⁷⁷⁵ A. A. Ziyaev, O. S. Otroshchenko, and A. S. Sadykov, *Zh. Obshch. Khim.* **34**, 351 (1964).

⁷⁷⁶ W. H. Taplin, U.S. Patent 3,420,833 (1969) [*CA* **71**, 3279 (1969)].

⁷⁷⁷ R. D. Chambers, D. Lomas, and W. K. R. Musgrave, *Tetrahedron* **24**, 5633 (1968).

chlorination of 2,2'-bipyridine gives 6-chloro- and 6,6'-dichloro-2,2'-bipyridines.⁷⁷⁸ Likewise, bromination of 2,2'-bipyridine in the vapor phase at 500°C gives 6-bromo- and 6,6'-dibromo-2,2'-bipyridines. 2,2':6',2''-Terpyridine similarly affords mono- and dibromo derivatives.⁴⁰⁸ At lower temperatures (250°C) bromination of 2,2'-bipyridine hydrobromide produces 5-bromo- and 5,5'-dibromo-2,2'-bipyridines.^{408,779} Sulfonation of 2,2'-bipyridine with sulfuric acid at 300°C affords 2,2'-bipyridine-5-sulfonic acid and 2,2'-bipyridine-5,5'-disulfonic acid.⁷⁸⁰ Sulfonation with sulfur trioxide at 200–225°C⁷⁸¹ or with oleum and a catalyst at 220°C⁷⁸² gives only the 5-sulfonic acid. As expected, reaction of 2,2'-bipyridine with aryllithiums^{409,522,783,784} or alkylolithiums^{784,785} affords 6-aryl- (or alkyl)- and 6,6'-diaryl- (or dialkyl)-2,2'-bipyridines, depending on reaction conditions. The comparative susceptibility of pyridine, 2,2'-bipyridine, 2,2':6',2''-terpyridine, and 3,3'- and 4,4'-bipyridines toward nucleophilic attack has been determined by reaction of mixtures of the compounds with butyllithium.⁷⁸⁶ 2,2'-Bipyridine reluctantly participates in the Chichibabin reaction with sodamide,⁷⁷² although a diaminobipyridine,⁴³⁹ subsequently shown to be 6,6'-diamino-2,2'-bipyridine,⁴⁰⁸ is formed. 2,2'-Bipyridine is converted to 4-methyl-2,2'-bipyridine by methyl radicals generated from tetramethyllead through an intermediate iron complex.⁷⁸⁷

Many of the substitution reactions of 2,3'-bipyridine have been conducted using anabasine (**12**: R = H) as starting material, which presumably is dehydrogenated to 2,3'-bipyridine prior to substitution. Chlorination of anabasine (as the hydrochloride) at 220–230°C affords 5-chloro-2,3'-bipyridine.⁷⁸⁸ Isoanabasine [2-(3-piperidyl)pyridine] behaves similarly on chlorination.⁵⁶⁸ 2,3'-Bipyridine is fully chlorinated to octachloro-2,3'-bipyridine by

⁷⁷⁸ S. H. Ruetman, U.S. Patent 3,819,558 (1974) [CA **81**, 91363 (1974)].

⁷⁷⁹ Y. V. Kurbatov, V. K. Kiryukhin, O. S. Otroshchenko, and A. S. Sadykov, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **286**, 92 (1966) [CA **67**, 82059 (1967)].

⁷⁸⁰ O. S. Otroshchenko, Y. V. Kurbatov, and A. S. Sadykov, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **263**, 27 (1964) [CA **63**, 4248 (1965)].

⁷⁸¹ Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* **263**, 36 (1964) [CA **63**, 8309 (1965)].

⁷⁸² N. H. Pirzada, P. M. Pojer, and L. A. Summers, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **31B**, 115 (1976).

⁷⁸³ R. F. Knott and J. G. Breckenridge, *Can. J. Chem.* **32**, 512 (1954).

⁷⁸⁴ T. Kauffmann, J. Koenig, and A. Woltermann, *Chem. Ber.* **109**, 3864 (1976).

⁷⁸⁵ K. J. Schmalzl and L. A. Summers, *Aust. J. Chem.* **30**, 657 (1977).

⁷⁸⁶ T. Kauffmann, J. Konig, D. Korber, and H. Lexy, *Tetrahedron Lett.*, 389 (1977).

⁷⁸⁷ K. L. Rollick and J. K. Kochi, *J. Org. Chem.* **47**, 435 (1982).

⁷⁸⁸ V. K. Kiryukhin, O. S. Otroshchenko, and A. S. Sadykov, *Khim. Geterosikl. Soedin.*, 370 (1965) [CA **63**, 13334 (1965)].

a vapor-phase reaction at 575°C.⁷⁸⁹ Anabasine and 2,3'-bipyridine, as expected, usually give 5-bromo-2,3'-bipyridine on bromination at about 220°C, but sometimes 5'-bromo- and 5,5'-dibromo-2,3'-bipyridines are obtained as well.^{566-568,790} Sulfonation of anabasine with sulfuric acid at 300°C results in the formation of 2,3'-bipyridine-5-sulfonic acid,⁵⁶⁴ but sulfonation of isoanabasine affords 2,3'-bipyridine-5'-sulfonic acid.⁵⁶⁵ Amination of 2,3'-bipyridine with sodamide gives several products including 4-amino-, 6-amino-, 2'-amino-, 4'-amino-, and 6'-amino-2,3'-bipyridines.^{791,792} Nitration of 2,3'-bipyridin-6'-one affords the 5-nitro derivative.⁵⁸⁸

Not much has been reported on substitution reactions of 2,4'-bipyridines. It is fully substituted to octachloro-2,4'-bipyridine on chlorination in the vapor phase at 575°C.⁷⁸⁹ Bromination of 3,3'-bipyridine at 250°C gives a 20% yield of 5-bromo-3,3'-bipyridine.⁷⁷⁹ Sulfonation at 220-320°C likewise affords 3,3'-bipyridine-5-sulfonic acid in yields up to 85%.^{773,781,793} A tetra-nitro derivative is obtained by nitration of 6,6'-diamino-3,3'-bipyridine,⁶²¹ whereas nitration of 3,3'-bipyridin-6-one affords the 5-nitro derivative.⁵⁸⁸ Amination of 3,3'-bipyridine affords 6-amino-3,3'-bipyridine.⁷⁹⁴ The only example of substitution of 3,4'-bipyridine involves sulfonation by sulfuric acid at 260°C to produce 3,4'-bipyridine-3'-sulfonic acid, the substitution taking place in the γ -pyridyl ring.⁷⁹⁵ 3,4'-Bipyridin-6-one is nitrated^{588,653} and formylated⁷⁹⁶ in the 5 position.

Complete chlorination of 4,4'-bipyridine to octachloro-4,4'-bipyridine is accomplished by vapor-phase chlorination at 555°C.⁷⁷⁶ Mono-, di-, tri-, and tetrachloro-4,4'-bipyridines substituted at the positions ortho to the nitrogen atoms are obtained at lower temperatures.^{778,797,798} 2,6-Dihydroxy-3-cyano-4,4'-bipyridine gives 2,5,6-trichloro-3-cyano-4,4'-bipyridine on reaction with phosphorus chlorides, ring substitution accompanying replacement

⁷⁸⁹ R. D. Bowden, British Patent 1,276,253 (1972) [CA 77, 61830 (1972)].

⁷⁹⁰ M. Goshayev, O. S. Otroshchenko, V. B. Leont'ev, and A. S. Sadykov, *Izv. Akad. Nauk Turkm. SSR, Ser. Fiz.-Tekh., Khim. Geol. Nauk*, 109 (1971) [CA 76, 85981 (1972)].

⁷⁹¹ D. A. Inoyatova, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* 167, 123 (1969) [CA 74, 125364 (1971)].

⁷⁹² D. A. Inoyatova and O. S. Otroshchenko, *Sb. Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* 539, 23 (1977) [CA 91, 175151 (1979)].

⁷⁹³ O. S. Otroshchenko, Y. V. Kurbatov, A. S. Sadykov, and F. Pirnazarova, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* 263, 33 (1964) [CA 63, 4248 (1965)].

⁷⁹⁴ D. A. Inoyatova, O. S. Otroshchenko, A. S. Sadykov, and A. K. Mamatkazina, *Tr. Samark. Gos. Univ. im. Alishera Navoi* 167, 173 (1969) [CA 74, 125360 (1971)].

⁷⁹⁵ O. S. Otroshchenko, A. A. Ziyaev, and A. S. Sadykov, *Nauchn. Tr.—Tashk. Gos. Univ. im. V. I. Lenina* 286, 85 (1966) [CA 67, 82057 (1967)].

⁷⁹⁶ G. Y. Leshner and C. J. Opalka, U.S. Patent 4,225,601 (1980) [CA 94, 83965 (1981)].

⁷⁹⁷ J. I. Darragh, British Patent 1,491,254 (1977) [CA 88, 190594 (1978)].

⁷⁹⁸ J. I. Darragh, British Patent 1,494,336 (1977) [CA 89, 24154 (1978)].

of hydroxyl with chlorine.⁶⁵⁰ Sulfonation of 4,4'-bipyridine at 200°C gives the 3-sulfonic acid⁷⁹⁹ and at 320°C the 3,3',5,5'-tetrasulfonic acid.⁷⁷⁴ Amination of 4,4'-bipyridine at 200°C with sodamide gives the expected 2,2'-diamino-4,4'-bipyridine,⁸⁰⁰ whereas alkylation with alkylolithiums affords 2-alkyl-4,4'-bipyridines.^{785,801} Alkylation of 4,4'-bipyridine with alkyl radicals generated from the silver-catalyzed decarboxylation of aliphatic acids by ammonium peroxydisulfate affords 2-alkyl-substituted 4,4'-bipyridines because of the nucleophilic character of the alkyl radicals.⁸⁰² In similar interesting free radical nucleophilic reactions, 4,4'-bipyridine may be substituted mainly in the 2,2',6,6' positions by alkyl or acyl groups, although some 3'-substitution also occurs. For example, acetyl radicals give various di-, tri-, and tetraacetyl substituted 4,4'-bipyridines.^{803,804} Oxidative coupling of *p*-dioxane or tetrahydrofuran with 4,4'-bipyridine in the presence of ammonium persulfate gave, for example, 2,2',6,6'-tetra(1,4-dioxanyl)-4,4'-bipyridine.⁸⁰⁵

D. REACTIONS AT NITROGEN

1. 2,2'-Bipyridine

a. *Quaternary Salts.* Monoquaternization of 2,2'-bipyridine with one equivalent of methyl iodide affords 1-methyl-2,2'-bipyridinium iodide (27),¹⁰⁷ and numerous other examples of monoquaternization with various alkyl halides and dimethyl sulfate have been reported.^{404,806-813} Substituted

⁷⁹⁹ A. A. Ziyaev, O. S. Otroschenko, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.*, 90 (1965) [*CA* 63, 5595 (1965)].

⁸⁰⁰ Chemische Fabrik auf Actien, E. Schering, H. Horsters, and M. Dohrn, German Patent 398,204 (1924) [*Chem. Zentralb.* II, 1409 (1924)].

⁸⁰¹ K. J. Schmalzl and L. A. Summers, *Chem. Ind. (London)*, 652 (1975).

⁸⁰² F. Minisci, F. Bertini, R. Galli, and A. Quilico, German Patent 2,153,234 (1972) [*CA* 77, 48278 (1972)].

⁸⁰³ T. Caronna, A. Citterio, T. Crolla, and F. Minisci, *Tetrahedron Lett.*, 1731 (1976).

⁸⁰⁴ A. Citterio, A. Arnoldi, and C. Macri, *Chim. Ind. (Milan)* 60, 14 (1978).

⁸⁰⁵ R. O. Kochkanyan, S. S. Lukanyuk, and S. V. Khripunov, *Khim. Geterotsikl. Soedin.*, 1134 (1980).

⁸⁰⁶ R. F. Homer and T. E. Tomlinson, *J. Chem. Soc.*, 2498 (1960).

⁸⁰⁷ I. C. Calder and W. H. F. Sasse, *Tetrahedron Lett.*, 3871 (1964).

⁸⁰⁸ D. H. Corr and E. E. Glover, *Chem. Ind. (London)*, 2128 (1964).

⁸⁰⁹ I. C. Calder and W. H. F. Sasse, *Tetrahedron Lett.*, 1465 (1965).

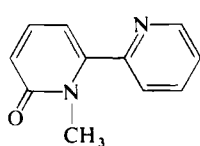
⁸¹⁰ D. H. Corr and E. E. Glover, *J. Chem. Soc.*, 5816 (1965).

⁸¹¹ I. C. Calder and W. H. F. Sasse, *Aust. J. Chem.* 21, 1023 (1968).

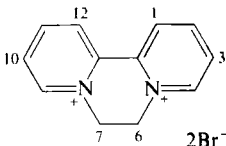
⁸¹² I. C. Calder and W. H. F. Sasse, *Aust. J. Chem.* 21, 2951 (1968).

⁸¹³ A. Calderbank, D. F. Charlton, J. A. Farrington, and R. James, *J. C. S. Perkin I*, 138 (1972).

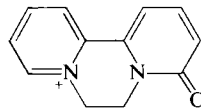
2,2'-bipyridines behave similarly.^{814,815} The kinetics of the methylation of 2,2'-bipyridine with methyl iodide in nonaqueous solvents have been studied.⁸¹⁶⁻⁸¹⁸ Oxidation of 1-methyl-2,2'-bipyridinium iodide (**77**) with ferricyanide affords the pyridone **74**, which reacts with a mixture of phosphorus pentachloride and phosphorus oxychloride to give 6-chloro-2,2'-bipyridine. 6-Bromo-2,2'-bipyridine is obtained similarly.⁸¹⁹ Oxidation of other monoquaternary salts in the same way has been described.⁸¹³ The sterically hindered salt 1-methyl-3,3'-dicarbomethoxy-2,2'-bipyridinium iodide has been resolved, and its racemization has been studied.^{404,820} 1-Methyl-2,2'-bipyridinium salts are demethylated by heating to 150°C and the kinetics of the reaction have been studied.⁸¹⁸ 1-Alkyl-4,6-diphenyl-2,2'-bipyridinium salts are available by reaction of 4,6-diphenyl-2-(2-pyridinio)pyrylium bis-(tetrafluoroborate) with primary amines.⁵¹² They participate in rearrangements and dealkylation on heating.



(74)



(75)



(76)

There has been considerable interest in diquaternary salts of 2,2'-bipyridine. Simple 1,1'-dialkyl-2,2'-bipyridinium salts are obtained by reaction of 2,2'-bipyridine with excess of an alkyl halide or dialkyl sulfate and related processes,^{84,102,211,821-825} and dialkyl diquaternary salts of substituted 2,2'-bipyridines are obtained likewise.^{404,826} Bridged diquaternary salts are formed by reaction of 2,2'-bipyridines with 1,2-dibromoethane. Thus the parent compound affords 6,7-dihydrodipyrido-[1,2-*a*:2',1'-*c*]pyrazinedium

⁸¹⁴ Australian National University, British Patent 956,848 (1964) [CA 62, 4032 (1965)].

⁸¹⁵ F. P. Dwyer, R. D. Wright, and A. Shulman, Australian Patent 251,598 (1964) [CA 66, 46417 (1967)].

⁸¹⁶ L. W. Deady and J. A. Zoltewicz, *J. Org. Chem.* **37**, 603 (1972).

⁸¹⁷ U. Berg, R. Gallo, G. Klatte, and J. Metzger, *J. C. S. Perkin II*, 1350 (1980).

⁸¹⁸ L. W. Deady, *Aust. J. Chem.* **34**, 163 (1981).

⁸¹⁹ F. H. Case, *J. Org. Chem.* **31**, 2398 (1966).

⁸²⁰ A. L. Stone and J. G. Breckenridge, *Can. J. Chem.* **30**, 725 (1952).

⁸²¹ F. G. Mann and J. Watson, *J. Org. Chem.* **13**, 502 (1948).

⁸²² H. C. Beyerman and J. S. Bontekoe, *Recl. Trav. Chim. Pays-Bas* **74**, 1395 (1955).

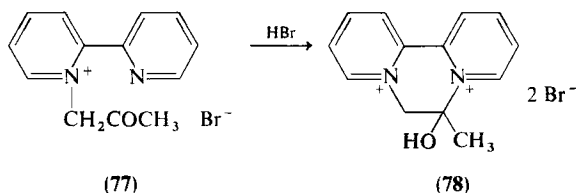
⁸²³ F. E. Cislak, U.S. Patent 3,049,547 (1962) [CA 59, 8712 (1963)].

⁸²⁴ L. A. Summers, *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **29B**, 89 (1974).

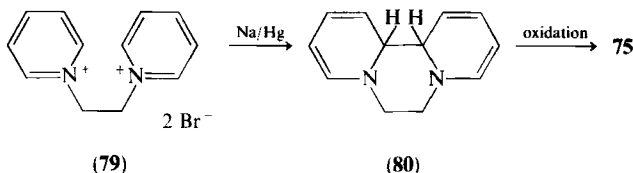
⁸²⁵ M. Yaguchi and A. Kato, Japanese Patent 105,179 (1977) [CA 88, 37629 (1978)].

⁸²⁶ M. Pitman and P. W. Sadler, *J. Chem. Soc.*, 759 (1961).

dibromide (**75**), which is the important herbicide diquat dibromide.^{806,827} Many analogs of **75** with substituents in the pyridine rings have also been prepared^{782,785,806,828-833} although 6-alkoxy-2,2'-bipyridines react with ethylene dibromide to afford the pyridone **76** rather than 4-alkoxy analogs of **75**.⁸²⁸ Derivatives of **75** with alkyl substituents on the ethylene bridge (i.e., 6 and/or 7 positions) can likewise be prepared from 2,2'-bipyridines and appropriate dibromoalkanes.⁸³⁴⁻⁸³⁸ 6-Hydroxy-substituted derivatives of **75**, for example, compound **78**, are accessible by ring closure of β -carbonyl monoquaternary salts of 2,2'-bipyridine, such as compound **77**, with acid,



and hydrazone and oxime derivatives of the carbonyl monoquaternary salts cyclize similarly.^{807-810,812,839} Related syntheses have been described for 6-methoxy substituted salts.⁵¹² Because of its importance, several other routes to diquat have been devised, involving reaction of 2,2'-bipyridine with ethylene and chlorine, with ethylene glycol, and with 2-bromoethanol and related reagents.⁴⁶⁷ Of some interest is the intramolecular coupling of the diquaternary salt **79**, using sodium amalgam, whereby diquat (**75**) is ob-



⁸²⁷ R. J. Fielden, R. F. Homer, and R. L. Jones, British Patent 785,732 (1957) [*CA* **52**, 6707 (1958)].

⁸²⁸ P. M. Pojer and L. A. Summers, *J. Heterocycl. Chem.* **11**, 303 (1974).

⁸²⁹ J. E. Dickeson and L. A. Summers, *Experientia* **25**, 1247 (1969).

⁸³⁰ T. M. Spotswood and C. I. Tanzer, *Aust. J. Chem.* **20**, 1213 (1967).

⁸³¹ R. F. Homer, British Patent 857,501 (1960) [*CA* **55**, 12430 (1961)].

⁸³² R. F. Homer, U.S. Patent 3,202,500 (1965) [*CA* **63**, 16368 (1965)].

⁸³³ Imperial Chemical Industries Ltd., French Addn. Patent 82,187 (1964) [*CA* **60**, 14521 (1964)].

⁸³⁴ D. J. Fry and B. A. Lea, British Patent 940, 152 (1963) [*CA* **60**, 155 (1964)].

⁸³⁵ A. L. Black and L. A. Summers, *J. Heterocycl. Chem.* **8**, 29 (1971).

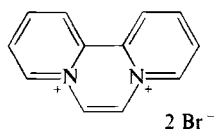
⁸³⁶ Imperial Chemical Industries Ltd., Netherlands Patent 6,406,225 (1964) [*CA* **63**, 13292 (1965)].

⁸³⁷ Imperial Chemical Industries Ltd., Belgian Patent 658,519 (1965) [*CA* **64**, 9691 (1966)].

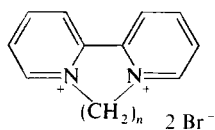
⁸³⁸ D. R. Douglas and G. F. Duffin, British Patent 946,476 (1964) [*CA* **60**, 10102 (1964)].

⁸³⁹ D. H. Corr and E. E. Glover, *Chem. Ind. (London)*, 847 (1965).

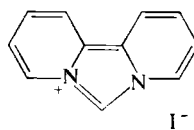
tained after oxidation of the intermediate **80**.⁸⁴⁰ Radioactive-labeled diquat dibromide has been synthesized.⁸⁴¹ The fully aromatic ring system dipyr-ido[1,2-*a*:2, 1'-*c*]pyrazinediium dibromide (**81**) is obtained by dehydration of the 6-hydroxy derivative of diquat with thionyl chloride,^{809,839} and various substituted derivatives of **81** have also been synthesized by similar routes.^{807,810,812,835} Homologs of diquat containing three (**82**; $n = 3$) or



(81)

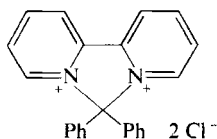


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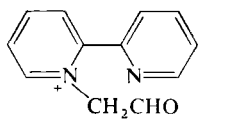


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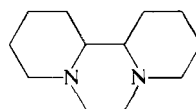
four (**82**; $n = 4$) methylene groups in the bridge have also been synthesized, using 1,3-dibromopropane^{782,785,806,830,842-845} and 1,4-dibromobutane,^{806,830,842} respectively, and several related diquaternary systems,^{842,846-848} including bridged salts containing nine- and ten-membered central rings, have been synthesized.⁸⁴⁸ The system **82** ($n = 1$), however, is stable only in strong acid solutions, and reaction of 2,2'-bipyridine with diiodomethane gives instead the monoquaternary system **83** and derivatives thereof.⁸⁴⁹ The diquaternary salt **84** is, however, obtained from 2,2'-bipyridine and dichlorodiphenylmethane.⁸⁵⁰ Further work on the synthesis and properties of analogs of **83** has been described.⁸¹¹



(84)



(85)



(86)

⁸⁴⁰ J. F. Cairns and J. A. Corran, German Patent 1,801,365 (1969) [CA 71, 81424 (1969)].

⁸⁴¹ M. J. Dunn, R. J. Martin, N. L. Roberts, P. Slade, H. Standen, and P. Walker, *J. Chem. Soc.*, 1468 (1966).

⁸⁴² F. D. Popp and D. K. Chesney, *J. Heterocycl. Chem.* **9**, 1165 (1972).

⁸⁴³ I. C. Calder, T. M. Spotswood, and C. I. Tanzer, *Aust. J. Chem.* **20**, 1195 (1967).

⁸⁴⁴ R. T. Salmon and F. M. Hawkrigide, *J. Electroanal. Chem. Interfacial Electrochem.* **112**, 253 (1980).

⁸⁴⁵ A. Launikonis, J. W. Loder, A. W. H. Mau, W. H. F. Sasse, L. A. Summers, and D. Wells, *Aust. J. Chem.* **35**, 1341 (1982).

⁸⁴⁶ I. C. Calder, W. H. F. Sasse, and T. M. Spotswood, *Aust. J. Chem.* **16**, 289 (1963).

⁸⁴⁷ F. Vogtle and H. Foerster, *Chem.-Ztg.* **97**, 386 (1973).

⁸⁴⁸ F. Vogtle and D. Brombach, *Chem. Ber.* **108**, 1682 (1975).

⁸⁴⁹ I. C. Calder, T. M. Spotswood, and W. H. F. Sasse, *Tetrahedron Lett.*, 95 (1963).

⁸⁵⁰ I. C. Calder, and W. H. F. Sasse, *Aust. J. Chem.* **18**, 1819 (1965).

The diquaternary salts of 2,2'-bipyridine frequently crystallize from aqueous solvents with water of crystallization, and many of the salts are hygroscopic. They are dissociated to positive and negative ions in aqueous solution and are strong electrolytes. Distribution of the positive charges in the diquat dication has been calculated by quantum mechanics.⁸⁵¹ Considerable work has been reported on the spectra of diquaternary salts of 2,2'-bipyridine. The UV absorption spectra of the 1,1'-dimethyl-2,2'-bipyridinium dication and three salts, diquat (**75**), **82** ($n = 3$), and **82** ($n = 4$) show that diquat (**75**) is the most conjugated since it absorbs at the longest wavelength. This is attributed to the ability of the two pyridine rings to adopt a nearly coplanar conformation in diquat, whereas in the salts **82** ($n = 3$) and **82** ($n = 4$) the extra methylene groups in the quaternizing bridge twist the two pyridine rings out of coplanar conformation. Similarly, the 1,1'-dimethyl-2,2'-bipyridinium dication is less conjugated than diquat because the methyl quaternizing groups sterically hinder the adoption of a coplanar conformation by the two pyridine rings.^{806,852} Further studies of the stereochemistry and conformation of diquaternary salts of 2,2'-bipyridine have been reported.^{806,830,843,848} The UV spectra of several other salts have been determined.^{782,806,809,810,812,829,830,835,843,846,850,853} The IR spectrum of diquat dibromide (**75**) has been interpreted.⁸⁵⁴ The proton NMR spectra of diquat (**75**) and the salts **82** ($n = 3$) and **82** ($n = 4$) and some of their dimethyl-substituted analogs have been completely analyzed, and from this work it has been deduced that in deuterium oxide solution the interplanar angle of the two pyridine rings in diquat is 9° ; in the salt **82** ($n = 3$) it is 60° , and in the salt **82** ($n = 4$) it is 80° .^{830,843,855} Several other examples of the proton NMR spectra of diquaternary salts of 2,2'-bipyridine have been reported.^{782,785,807,809,810,812,828,829,835,839,843,846,848,849} The ^{13}C -NMR spectrum⁸⁵⁶ and the field desorption mass spectrum of diquat dibromide (**75**) have also been published.⁸⁵⁷ Secondary ion mass spectra of diquat dibromide and 1,1'-dimethyl-2,2'-bipyridinium salts⁸⁵⁸ and off-line combination of isotachopheresis and mass spectrometry have been investigated.⁸⁵⁹ High resolution X-ray diffraction analysis of the diquat dication (**75**) con-

⁸⁵¹ J. Burdon, M. H. B. Hayes, and M. E. Pick, *J. Environ. Sci. Health, Part B* **B12**, 37 (1977).

⁸⁵² R. F. Homer, G. C. Mees, and T. E. Tomlinson, *J. Sci. Food Agric.* **11**, 309 (1960).

⁸⁵³ B. Kok, H. J. Rurainski, and O. V. H. Owens, *Biochim. Biophys. Acta* **109**, 347 (1965).

⁸⁵⁴ R. Haque and S. Lilley, *J. Agric. Food Chem.* **20**, 57 (1972).

⁸⁵⁵ R. Haque, W. R. Coshaw, and L. F. Johnson, *J. Am. Chem. Soc.* **91**, 3822 (1969).

⁸⁵⁶ K. R. Long, R. C. Long, and J. H. Goldstein, *J. Magn. Reson.* **8**, 207 (1972).

⁸⁵⁷ J. F. J. Hughes, N. Evans, D. E. Games, M. J. E. Hewlins, A. H. Jackson, J. R. Jackson, N. A. Khan, S. A. Matlin, M. Rossiter, R. G. Saxton, H. A. Swaine, and K. T. Taylor, *Adv. Mass Spectrom. Biochem. Med.* **1**, 357 (1976).

⁸⁵⁸ T. M. Ryan, R. J. Day, and R. G. Cooks, *Anal. Chem.* **52**, 2054 (1980).

⁸⁵⁹ E. Kenndler and D. Kaniansky, *J. Chromatogr.* **209**, 306 (1981).

firmly that the two pyridine rings are nearly coplanar with a dihedral angle between the planes of the pyridine rings of about 20° ,⁸⁶⁰⁻⁸⁶² whereas in the salt **82** ($n = 4$) the dihedral angle, as expected, is much greater—about 66° .⁸⁶³

Several reactions of diquaternary salts of 2,2'-bipyridine have been investigated. As expected, the salts are much more stable in acid solution than in base. Diquat dibromide decomposes in strong alkaline solution, and other salts behave likewise. The 4-bromo analog of diquat is particularly susceptible to hydroxyl ions, forming the pyridone **76** at pH values above 5.0,⁸²⁸ and 6-hydroxy derivatives are stable only below about pH 4.0, being in reversible equilibrium with aldehyde forms such as **85**, which predominate above that pH value.^{812,864} Catalytic hydrogenation of **75** with Raney nickel affords the fully hydrogenated species **86**,⁸⁶⁵ which is also obtained by hydrogenation of the fully aromatic system **81**.^{809,810,839} When **75** is hydrogenated, using platinum oxide⁸⁶⁶ or sodium borohydride and nickel chloride catalyst,⁸⁶⁷ the same compound (**86**) is obtained that was shown by gas-liquid chromatography to consist of two isomers possibly with the hydrogens on the central bond in the cis or trans configurations. Several hydrogenations of other diquaternary salts with similar results have been reported.^{807,810,812,842,845} Reduction of **75** by sodium amalgam⁸⁴⁰ or sodium borohydride^{868,869} gives partly hydrogenated derivatives.

The one-electron reduction of diquaternary salts of 2,2'-bipyridine has attracted much attention. When an aqueous solution of diquat dibromide (**75**) is treated with a one-electron reducing agent, such as zinc dust, the solution acquires an intense green color. This is due to the formation of the stable radical cation **87**. The one-electron transfer is completely reversed by air. In theory the radical cation **87** can take up another electron to form the neutral species **88**. The stability of the radical cation **87** is due to the ability of the odd electron to be located at any of the nuclear positions because of the near coplanarity of the two pyridine rings.^{852,870} The potential E_0 of the first one-electron transfer occurs at -0.35 V in aqueous solution

⁸⁶⁰ J. E. Derry and T. A. Hamor, *Nature (London)* **221**, 464 (1969).

⁸⁶¹ P. D. Sullivan and M. L. Williams, *J. Am. Chem. Soc.* **98**, 1711 (1976).

⁸⁶² T. Sundaresan and S. C. Wallwork, *Acta Crystallogr. Sect. B* **B28**, 3065 (1972).

⁸⁶³ J. E. Derry and T. A. Hamor, *J. C. S. Chem. Commun.*, 1284 (1970).

⁸⁶⁴ A. L. Black and L. A. Summers, *J. Chem. Soc. C*, 610 (1969).

⁸⁶⁵ R. C. Brian, R. F. Homer, J. Stubbs, and R. L. Jones, *Nature (London)* **181**, 446 (1958).

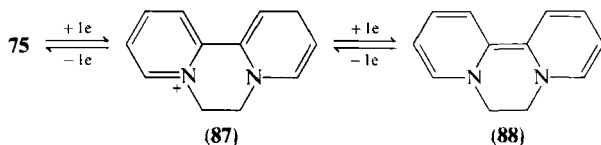
⁸⁶⁶ C. J. Soderquist and D. G. Crosby, *Bull. Environ. Contam. Toxicol.* **8**, 363 (1972).

⁸⁶⁷ S. Ukai, K. Hirose, and S. Kawase, *Eisei Kagaku* **23**, 32 (1977).

⁸⁶⁸ S. Ukai, K. Hirose, and S. Kawase, *Eisei Kagaku* **19**, 281 (1973).

⁸⁶⁹ G. H. Draffan, R. A. Clare, D. J. Davies, G. Hawksorth, S. Murray, and D. S. Davies, *J. Chromatogr.* **139**, 311 (1977).

⁸⁷⁰ R. F. Homer and T. E. Tomlinson, *Nature (London)* **184**, 2012 (1959).



and is independent of pH because no hydrogen is involved. The second one-electron transfer occurs at lower potential (~ -0.75 V) as measured by polarography.^{211,806,852,870-876} The salts **82** ($n = 3$)^{211,806,852,874,876,877} and **82** ($n = 4$)^{806,874,876} and the 1,1'-dimethyl-2,2'-bipyridinium dication^{211,824,875,878} are reduced at lower potentials than that for diquat because the two pyridine rings are no longer coplanar. In the case of the last two salts, the one-electron transfer between the salt and its radical cation is not completely reversible. The reduction potentials of many substituted diquatertiary salts of 2,2'-bipyridine have also been measured.^{782,785,806,828,829,835,845,848,852,853,864,877} Diquat (75) and some of its relatives have been included in theoretical studies of redox equilibria.^{211,875,879} Further studies of the polarography of diquatertiary salts of 2,2'-bipyridine, including work in nonaqueous systems, have been described.^{211,383,844,871,874,875,880-882}

The UV absorption spectra of radical cations such as **87** have received attention,^{853,872,883-887} and the ESR spectra have been studied and in some cases interpreted.^{782,861,878,888,889} Rate constants for the one-electron reduction of diquat and the salts **82** ($n = 3$) and **82** ($n = 4$) have been determined by pulse radiolysis,⁸⁸⁶ and kinetic studies involving reactions of the diquat radical cation at hydrogen-evolving metal electrodes have been

⁸⁷¹ J. Engelhardt and W. P. McKinley, *J. Agric. Food Chem.* **14**, 377 (1966).

⁸⁷² C. C. Black, *Science* **149**, 62 (1965).

⁸⁷³ L. A. Summers, *Nature (London)* **214**, 381 (1967).

⁸⁷⁴ J. Volke and V. Volkova, *Collect. Czech. Chem. Commun.* **34**, 2037 (1969).

⁸⁷⁵ S. Hunig and J. Gross, *Tetrahedron Lett.*, 2599 (1968).

⁸⁷⁶ J. Volke, *Collect. Czech. Chem. Commun.* **33**, 3044 (1968).

⁸⁷⁷ C. C. Black, *Biochim. Biophys. Acta* **120**, 332 (1966).

⁸⁷⁸ L. A. Summers, *Naturwissenschaften* **54**, 491 (1967).

⁸⁷⁹ P. Carsky, S. Hunig, D. Scheutzw, and R. Zahradnik, *Tetrahedron* **25**, 4781 (1969).

⁸⁸⁰ L. Pospisil, J. Kuta, and J. Volke, *J. Electroanal. Chem. Interfacial Electrochem.* **58**, 217 (1975).

⁸⁸¹ A. Ledwith, in "Biochemical Mechanisms of Paraquat Toxicity" (A. P. Autor, ed.), pp. 21-28. Academic Press, New York, 1977.

⁸⁸² E. Amouyal, B. Zidler, P. Keller, and A. Moradpour, *Chem. Phys. Lett.* **74**, 314 (1980).

⁸⁸³ A. Calderbank, *Adv. Pest Control Res.* **8**, 127-235 (1968).

⁸⁸⁴ A. Calderbank, C. B. Morgan, and S. H. Yuen, *Analyst* **86**, 569 (1961).

⁸⁸⁵ R. W. Jones and P. B. Garland, *Biochem. J.* **164**, 199 (1977).

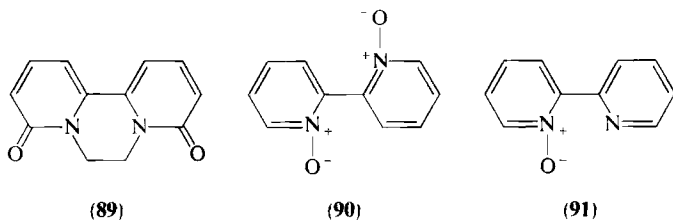
⁸⁸⁶ R. F. Anderson, *Ber. Bunsenges Phys. Chem.* **80**, 969 (1976).

⁸⁸⁷ A. G. Evans, R. E. Alford, and N. H. Rees, *J. C. S. Perkin II*, 445 (1977).

⁸⁸⁸ P. D. Sullivan, J. Y. Fong, M. L. Williams, and V. D. Parker, *J. Phys. Chem.* **82**, 1181 (1978).

⁸⁸⁹ R. S. Davidson and R. M. Slater, *J. C. S. Faraday I* **72**, 2416 (1976).

reported.⁸⁹⁰ Considerable interest has focused on the reaction of the diquat radical cation **87** with oxygen. In the oxidation of **87** back to diquat (**75**), oxygen is converted to the superoxide radical anion, O_2^- , which is thought to be an important species responsible for the herbicidal and toxic properties of diquat.^{887,891-894} The oxidation of **87** with several peroxides has also been studied.⁸⁹⁵ A few other reactions of diquaternary salts of 2,2'-bipyridine have been reported. Oxidation of diquat dibromide (**75**) with alkaline ferricyanide affords the dione **89**,⁸¹³ and other diquaternary salts behave similarly.^{842,896} 1,1'-Dimethyl-2,2'-bipyridinium bis(methylsulfate), for instance, gives 1,1'-dimethyl-2,2'-bipyridine-6,6'-(1*H*,1'*H*)-dione, which reacts with phosphorus halides to afford 6,6'-dichloro-2,2'-bipyridine.⁸⁹⁷ The diquat dication (**75**) and other salts of 2,2'-bipyridine are electron acceptors. In the presence of certain electron donors, such as iodide ions and 7,7,8,8-tetracyanoquinodimethane, they form charge-transfer complexes with the donor.^{854,855,862,898} The sterically hindered salt 1,1'-dimethyl-3,3'-dimethoxycarbonyl-2,2'-bipyridinium diiodide has been resolved.⁴⁰⁴ Diquat dibromide (**75**) can act as an oxidizing agent for the conversion of primary and secondary alcohols to the corresponding carbonyl compounds in the presence of UV irradiation,⁸⁹⁹ and related oxidations have been reported.⁹⁰⁰ The fate of diquat dibromide (**75**), including its photochemical decomposition and the methods of analysis of the herbicide, have been fully reviewed.⁴⁶⁷ To conclude the section on diquaternary salts of 2,2'-bipyridine, we record the formation of 1,1'-diamino-2,2'-bipyridinium salts by reaction



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⁸⁹¹ T. C. Stancliffe and A. Pirie, *FEBS Lett.* **17**, 297 (1971).

⁸⁹² B. L. Epel and J. Neumann, *Biochim. Biophys. Acta* **325**, 520 (1973).

⁸⁹³ J. F. Allen and D. O. Hall, *Biochem. Biophys. Res. Commun.* **52**, 856 (1973).

⁸⁹⁴ E. F. Elstner and A. Heupel, *Z. Naturforsch., C: Biosci.* **29C**, 559 (1974).

⁸⁹⁵ G. Levey, A. L. Rieger, and J. O. Edwards, *J. Org. Chem.* **46**, 1255 (1981).

⁸⁹⁶ L. Bauer, C. L. Bell, and G. E. Wright, *J. Heterocycl. Chem.* **3**, 393 (1966).

⁸⁹⁷ S. Ogawa and S. Shiraishi, *J. C. S. Perkin I*, 2527 (1980).

⁸⁹⁸ D. S. Acker and D. C. Blomstrom, U.S. Patent 3,162,641 (1964) [*CA* **63**, 549 (1965)].

⁸⁹⁹ A. S. Hopkins, A. Ledwith, and M. F. Stam, *J. C. S. Chem. Commun.*, 494 (1970).

⁹⁰⁰ J. R. Barnett, A. S. Hopkins, and A. Ledwith, *J. C. S. Perkin II*, 80 (1973).

of 2,2'-bipyridines with *O*-mesitylenesulfonylhydroxylamine.⁹⁰¹ These salts are acylated with benzoyl chloride and participate in 1,3-dipolar cycloadditions with dimethyl acetylenedicarboxylate.

b. *N*-Oxides. Reaction of 2,2'-bipyridine with excess hydrogen peroxide in glacial acetic acid affords 2,2'-bipyridine 1,1'-dioxide (90)^{772,902-904} with some of the 1-oxide 91 usually being formed as well.^{902,904,905} Caution should be exercised in distilling these reaction mixtures because explosions may result.⁹⁰⁶ 2,2'-Bipyridine 1-oxide is better prepared by reaction of 2,2'-bipyridine with 3-chloroperbenzoic acid,⁹⁰⁷ although with this reagent 1,1'-dioxides may also be obtained.⁴²¹ The sterically hindered 4,6-diphenyl-2,2'-bipyridine and related compounds are preferentially converted to the 1'-oxides.⁷²⁵ In another reaction, lithiopyridine 1-oxide and bromine at -65°C gave some 6,6'-dibromo-2,2'-bipyridine 1,1'-dioxide as well as the corresponding 1-oxide, and related compounds behaved similarly.^{908,909} Some 2,2'-bipyridine 1-oxide has been isolated from the decomposition of 2-aminopyridine in the presence of isoamyl nitrite.⁵³⁵ The *N*-oxides are converted back to 2,2'-bipyridine by a variety of reagents such as phosphorus trichloride and hydrogen iodide,^{772,910} whereas the natural product orellanine (9) is deoxygenated at the nitrogens by heat or by catalytic hydrogenation.¹¹ 2,2'-Bipyridine 1,1'-dioxide has been used as a dehydrogenating agent and in the process is reduced to 2,2'-bipyridine.⁹¹¹ The IR spectra⁹¹²⁻⁹¹⁷ of 2,2'-bipyridine 1-oxide and 1,1'-dioxide and their salts

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⁹⁰² I. Murase, *Nippon Kagaku Zasshi* **77**, 682 (1956).

⁹⁰³ P. G. Simpson, A. Vinciguerra, and J. V. Quagliano, *Inorg. Chem.* **2**, 282 (1963).

⁹⁰⁴ N. S. Bazhenova, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **206**, 226 (1972) [*CA* **80**, 95678 (1974)].

⁹⁰⁵ I. Antonini, F. Claudi, G. Cristalli, P. Franchetti, M. Grifantini, and S. Martelli *J. Med. Chem.* **24**, 1181 (1981).

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⁹¹¹ Y. V. Kurbatov, A. S. Kurbatova, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 33 (1969) [*CA* **74**, 99820 (1971)].

⁹¹² H. Shindo, *Chem. Pharm. Bull.* **6**, 117 (1958).

⁹¹³ A. Vinciguerra, P. G. Simpson, Y. Kakiuti, and J. V. Quagliano, *Inorg. Chem.* **2**, 286 (1963).

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⁹¹⁵ Z. Dega-Szafran, *Rocz. Chem.* **44**, 2371 (1970).

⁹¹⁶ G. V. Kireev, V. B. Leont'ev, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Dokl. Akad. Nauk Uzb. SSR*, 43 (1977) [*CA* **89**, 14241 (1978)].

⁹¹⁷ G. V. Kireev, V. B. Leont'ev, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1034 (1980) [*CA* **93**, 149227 (1980)].

have been thoroughly investigated, and the proton NMR,⁹¹⁸⁻⁹²⁰ ¹³C NMR,^{921,922} ¹⁴N NMR,⁹²³ photoelectron,¹⁵¹ UV,^{917,924} and mass spectra⁵³⁵ have been studied. The polarography^{902,910,925} and thin layer chromatography^{361,362,926} have also received attention. The structure of a 2,2'-bipyridine 1,1'-dioxide complex has been determined by X-ray crystallography.⁹²⁷

Some reactions of 2,2'-bipyridine *N*-oxides have been reported. The 1,1'-dioxide is nitrated readily to 4,4'-dinitro-2,2'-bipyridine 1,1'-dioxide.^{250,772,902,904} 2,2'-Bipyridine 1-oxide is also nitrated in the 4 position.^{250,904} The nitro groups in 4,4'-dinitro-2,2'-bipyridine 1,1'-dioxide are reactive, being replaced by chlorine with concentrated hydrochloric acid,^{772,928} by bromine with acetyl bromide,⁹²⁸ by hydroxyl with dilute sulfuric acid,⁷⁷² and by alkoxy groups with sodium alkoxides.^{772,928,929} Some of the dialkoxy derivatives are useful catalysts for the oxidation of aromatic compounds.⁹³⁰ The dinitro dioxide is deoxygenated to 4,4'-dinitro-2,2'-bipyridine with phosphorus trichloride in chloroform, and other substituted 1,1'-dioxides behave similarly,^{902,928} but with phosphorus trichloride alone, 4,4'-dichloro-2,2'-bipyridine results. The dinitro dioxide is reduced by iron powder in acetic acid to 4,4'-diamino-2,2'-bipyridine,⁹²⁸ whereas 4,4'-dichloro-2,2'-bipyridine 1,1'-dioxide is converted to its 4,4'-diamino analogs with amines.⁹²⁸ Related reactions have been described.⁷⁷²

Similar series of reactions have been described with 4-nitro-2,2'-bipyridine 1-oxide.^{250,904,929} 2,2':6',2"-Terpyridine tri-*N*-oxide has also been prepared

⁹¹⁸ V. B. Leont'ev, F. G. Kamaev, Y. V. Kurbatov, G. V. Kireev, O. S. Otroshchenko, and A. S. Sadykov, *Dokl. Akad. Nauk Uzb. SSR* **29**, 43 (1972) [*CA* **78**, 22143 (1973)].

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⁹²² G. V. Kireev, V. B. Leont'ev, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1645 (1978) [*CA* **89**, 162871 (1978)].

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⁹²⁴ G. V. Kireev, V. B. Leont'ev, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Dokl. Akad. Nauk Uzb. SSR*, 42 (1977) [*CA* **88**, 128611 (1978)].

⁹²⁵ V. B. Leont'ev, Y. V. Kurbatov, D. M. Ivinskii, E. Tuichiev, G. V. Kireev, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **206**, 52 (1972) [*CA* **80**, 132508 (1974)].

⁹²⁶ M. Bieganowska and T. Wawrzynowicz, *Chem. Anal. (Warsaw)* **24**, 887 (1979).

⁹²⁷ A. R. Al-Karaghoul, R. O. Day, and J. S. Wood, *Inorg. Chem.* **17**, 3702 (1978).

⁹²⁸ G. Maerker and F. H. Case, *J. Am. Chem. Soc.* **80**, 2745 (1958).

⁹²⁹ J. Skarzewski and J. Mlochowski, *Heterocycles* **12**, 1403 (1979).

⁹³⁰ J. Skarzewski, *J. Chem. Res., Synop.*, 410 (1980).

and converted to its trinitro derivative, which participates in similar replacement reactions.⁹³¹ 2,2'-Bipyridine 1-oxides are readily converted to 6-cyano-2,2'-bipyridines, using an alkylating (or acylating) reagent and potassium cyanide.^{7,905} 2,2'-Bipyridine 1,1'-dioxide with acetic anhydride affords 6,6'-diacetoxy-2,2'-bipyridine,⁹⁰² and 2,2'-bipyridine 1-oxide behaves similarly. The 6-acetoxy-2,2'-bipyridine produced is readily hydrolyzed to 6-hydroxy-2,2'-bipyridine.⁹³² Complexes of 2,2'-bipyridine 1,1'-dioxide with iodine have been studied.⁹³³ The UV and IR spectra of several substituted 2,2'-bipyridine 1-oxides have been studied and their ionization constants have been discussed.²⁵⁰ Studies on the polarography of some of these substituted *N*-oxides have also been reported.⁹³⁴

c. *Other Reactions.* To complete the section on 2,2'-bipyridine, we note the formation of *N*-alkyl-2,2'-bipyridones by condensation routes similar to those referred to in Section III,A,^{551,935} the synthesis of 1,1'-dimethyl-2,2'-bipyridin-6,6'-dione as a by-product of the reaction of benzyne generated from chlorobenzene and sodamide with 1-methyl-2-pyridone,⁸⁹⁶ and the formation of highly substituted 1-methyl-2,2'-bipyridin-6-ones by the hydrogenation of fused isoxazole derivatives.^{936,937}

2. 2,3'-Bipyridine

a. *Quaternary Salts.* Monoquaternization of 2,3'-bipyridine with methyl iodide affords 1'-methyl-2,3'-bipyridinium iodide, methylation occurring on the β -pyridyl ring,^{44,554,759} and various other similar monoquaternary salts have been prepared.^{554,564,938} 1'-Methyl-2,3'-bipyridinium iodide is oxidized by permanganate to picolinic acid⁷⁵⁹ and fully reduced in the β -pyridyl ring only by tin and hydrochloric acid⁷⁵⁹ and by formic acid and potassium formate.⁵⁵⁴ By ferricyanide oxidation the 6'-pyridone is formed from quaternary salts of this type.⁹³⁸ Under more vigorous conditions and with excess methyl iodide the diquaternary salt 1,1'-dimethyl-2,3'-bipyridinium diiodide is obtained from 2,3'-bipyridine.^{102,759} The UV spectrum has been recorded.¹⁰² Other diquaternary salts have been prepared.⁸²³

⁹³¹ F. H. Case, *J. Org. Chem.* **27**, 640 (1962).

⁹³² T. Mukaiyama, F. C. Pai, M. Onaka, and K. Narasaka, *Chem. Lett.*, 563 (1980).

⁹³³ U. Muralikrishna and N. S. Rao, *J. Indian Chem. Soc.* **57**, 524 (1980).

⁹³⁴ S. S. Katiyar, M. Lalithambika, and R. P. Shulka, *Bull. Chem. Soc. Jpn.* **45**, 685 (1972).

⁹³⁵ K. W. Merz and K. Rauchle, *Arch. Pharm. (Weinheim Ger.)* **293**, 968 (1960).

⁹³⁶ J. Nadelson, U.S. Patent 4,064,251 (1977) [*CA* **88**, 120994 (1978)].

⁹³⁷ J. Nadelson, U.S. Patent 4,124,714 (1978) [*CA* **90**, 87293 (1979)].

⁹³⁸ S. Sugawara and N. Saito, *J. Pharm. Soc. Jpn.* **68**, 93 (1948).

1-Alkyl-4,6-diphenyl-2,3'-bipyridinium salts are obtained by reaction of 2,4-diphenyl-6-(3-pyridyl)pyrylium perchlorate with primary amines. They form the 1'-methyl diquaternary salt with methyl iodide. Related syntheses were described.⁵¹² 2,3'-Bipyridine is reported to give a 1-tosylimide by reaction with hydroxylamine *O*-sulfonic acid followed by tosyl chloride. The tosyl-imide is a dehydrogenating agent.⁹³⁹

b. *N*-Oxides. 2,3'-Bipyridine with excess hydrogen peroxide and glacial acetic acid affords 2,3'-bipyridine 1,1'-dioxide,⁹⁴⁰ which on nitration gives 4-nitro-2,3'-bipyridine 1,1'-dioxide. This compound reacts with sodium ethoxide to give 4-ethoxy-2,3'-bipyridine 1,1'-dioxide and hence with phosphorus trichloride in chloroform to afford 4-ethoxy-2,3'-bipyridine.⁹⁴⁰ Related reactions on the labile nitro group have been described.^{941,942} 4-Nitro-2,3'-bipyridine 1,1'-dioxide is reduced by iron powder and acetic acid to 4-amino-2,3'-bipyridine.⁹⁴³ 2,3'-Bipyridine 1,1'-dioxide on bromination in chloroform gives 5'-bromo-2,3'-bipyridine 1,1'-dioxide along with a small amount of the deoxygenated product 5'-bromo-2,3'-bipyridine.⁹⁴⁴ 2,3'-Bipyridine 1,1'-dioxide has been used as a dehydrogenating agent.⁹¹¹ The mono-*N*-oxides 2,3'-bipyridine 1-oxide and 2,3'-bipyridine 1'-oxide are both accessible by controlled oxidation of 2,3'-bipyridine by hydrogen peroxide in acetic acid, the former being obtained at 80°C and the latter at 60°C.⁹⁴⁵ 2,3'-Bipyridine 1-oxide is nitrated to 4-nitro-2,3'-bipyridine 1-oxide, which can be deoxygenated to 4-nitro-2,3'-bipyridine,⁹⁴³ whereas 2,3'-bipyridine 1'-oxide on attempted nitration gave 2,3'-bipyridine.⁹⁴⁶ 2,3'-Bipyridine 1'-oxide on bromination gives a low yield of 5'-bromo-2,3'-bipyridine 1'-oxide along with 2,3'-bipyridine,⁹⁴⁴ whereas 2,3'-bipyridine

⁹³⁹ Y. V. Kurbatov, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.*, 225 (1975).

⁹⁴⁰ Y. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and S. V. Abdullaev, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 43 (1969) [*CA* **75**, 48836 (1971)].

⁹⁴¹ S. V. Abdullaev, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 52 (1969) [*CA* **74**, 125365 (1971)].

⁹⁴² S. V. Abdullaev and A. Irisbaev, *Master. Resp. Nauchno-Tekh. Konf. Molydykh Uch. Pererab. Nefti Neftekhim.*, 2nd., 1974, 168 (1974) [*CA* **85**, 77980 (1976)].

⁹⁴³ S. V. Abdullaev, Y. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and M. F. Khatamova, *Khim. Geterotsikl. Soedin.*, 381 (1973).

⁹⁴⁴ S. V. Abdullaev, Y. V. Kurbatov, V. S. Tsukervanik, O. S. Otroshchenko, A. S. Sadykov, and F. M. Khatamova, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **206**, 212 (1972) [*CA* **80**, 108322 (1974)].

⁹⁴⁵ Y. V. Kurbatov, S. V. Abdullaev, A. S. Kurbatova, O. S. Otroshchenko, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.*, 378 (1973).

⁹⁴⁶ Y. V. Kurbatov, S. V. Abdullaev, N. S. Bazhenova, O. S. Otroshchenko, and A. S. Sadykov, *Tezisy Vses. Soveshch. Khim. Nitrosoedin.*, 5th, 1974, 38 (1974) [*CA* **86**, 189668 (1977)].

1-oxide gave a dibromo derivative.⁹⁴⁷ The spectra of the *N*-oxides have been well studied, proton NMR,⁹¹⁸⁻⁹²⁰ ¹³C NMR,^{921,922} UV,^{917,924} and IR^{916,917} having all been investigated. Their polarographic behavior has also been reported.⁹²⁵

c. *Other Reactions.* *N*-alkyl 2,3'-bipyridinones have been prepared by condensation routes similar to those already described for 2,3'-bipyridinones^{935,948}

3. 2,4'-Bipyridine

Very little has been reported regarding 2,4'-bipyridine. As expected, it is quaternized preferentially on the γ -pyridyl ring⁹⁴⁹ and with excess methyl iodide the diquaternary salt 1,1'-dimethyl-2,4'-bipyridinium diiodide is obtained.^{91,102} The latter salt, like diquat, is reduced to a radical cation by one-electron reducing agents. The potential E_0 of the one-electron transfer in aqueous solution is -0.64 V.^{852,870} *N*-alkyl-2,4'-bipyridinones have been prepared by condensation routes starting from pyridine-4-aldehyde, and some of their reactions have been studied,⁹³⁵ whereas cyano-substituted 1'-aryl-2'-imino-2,4'-bipyridines have been obtained starting from pyridine-2-aldehyde, malononitrile, and amidines.⁹⁵⁰

4. 3,3'-Bipyridine

a. *Quaternary Salts.* Mono-^{573,951,952} and diquaternary^{102,211,573,951} salts of 3,3'-bipyridine have been prepared from alkyl halides and other quaternizing agents under appropriate conditions. They are oxidized by alkaline ferricyanide to the 6-one and 6,6'-dione, respectively,⁹⁵¹ further reactions of which were reported. The polarography of the 1,1'-dimethyl-3,3'-bipyridinium dication has been studied.²¹¹ 3,3'-Bipyridine gives a 1,1'-bis-(tosylimide) by reaction with hydroxylamine-*O*-sulfonic acid followed by tosyl chloride. The bisimide is a dehydrogenating agent.⁹³⁹

⁹⁴⁷ S. V. Abdullaev, V. S. Tsukervanik, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Tezisy Dokl.—Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop*, 2nd, 1973, 11 (1973) [*CA* **86**, 29588 (1977)].

⁹⁴⁸ R. F. Borch, C. V. Grudzinskas, D. A. Peterson, and L. D. Weber, *J. Org. Chem.* **37**, 1141 (1972).

⁹⁴⁹ H. Fischer and L. A. Summers, *J. Heterocycl. Chem.* **17**, 333 (1980).

⁹⁵⁰ S. Robev, *Heterocycles* **14**, 461 (1980).

⁹⁵¹ S. Sugawara and T. Saito, *J. Pharm. Soc. Jpn.* **65**, 6 (1945).

⁹⁵² N. S. Bazhenova, Y. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and V. Ruzanov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **206**, 234 (1972) [*CA* **80**, 108320 (1974)].

b. *N-Oxides*. The 1-oxide⁹⁵³ or the 1,1'-dioxide^{80,910,953} are obtained from 3,3'-bipyridine on reaction with hydrogen peroxide in acetic acid under appropriate conditions. Unlike the *N*-oxides of the other bipyridines, attempts to nitrate the *N*-oxides of 3,3'-bipyridine result in deoxygenation instead of nitration.^{953,954} 4,4'-Dinitro-3,3'-bipyridine 1,1'-dioxide, however, has recently been obtained by an Ullmann reaction on 3-bromo-4-nitropyridine *N*-oxide. It is reduced by zinc and sulfuric acid to 4,4'-diamino-3,3'-bipyridine.⁹⁵⁵ Bromination of the 1-oxide, however, affords some 5-bromo-3,3'-bipyridine 1-oxide along with deoxygenated products,^{952,954} and the 1,1'-dioxide is likewise brominated in positions β to the *N*-oxide groups.^{624,954} The brominated *N*-oxides are reduced by iron powder in acetic acid to the appropriate bromo- or dibromo-3,3'-bipyridines.^{624,952} 3,3'-Bipyridine 1,1'-dioxide gives a bispyridone with acetic anhydride,⁸⁰ is deoxygenated with sulfur dioxide,⁹¹⁰ and can be used as a dehydrogenating agent.⁹¹¹ The IR,^{912,916,917} UV,^{917,924} proton NMR,⁹¹⁸⁻⁹²⁰ and ¹³C NMR^{921,922} spectra have all been investigated, and studies on the polarography⁹²⁵ of the *N*-oxides have been reported.

c. *Other Reactions*. In a reaction akin to some reactions covered in Section III,D, 1-methyl-5-methoxypyridin-2-one coupled oxidatively with bromine water to give an analog of **59**.⁶³⁷ 1,1'-Diethyl-3,3'-bipyridine-6,6'-dione is formed as a by-product during the Friedel-Crafts cyclohexylation of 1-ethylpyridin-2-one.⁹⁵⁶

5. 3,4'-Bipyridine

1,1'-Dimethyl-3,4'-bipyridinium bis(tetrafluoroborate) has been prepared from 3,4'-bipyridine and trimethyloxonium tetrafluoroborate, and its polarography has been studied.²¹¹ A 1'-oxide of a substituted 3,4'-bipyridin-6-one has been prepared.⁹⁵⁷ The 1-methyl analog of the pyridone **66** was obtained in the same way as **66** using *N*-methylcyanoacetamide instead of cyanoacetamide.⁶⁵⁴

⁹⁵³ Y. V. Kurbatov, N. S. Bazhenova, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 57 (1969) [*CA* **75**, 98409 (1971)].

⁹⁵⁴ N. S. Bazhenova, Y. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Tezisy Dokl.—Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop.*, 2nd, 1973, 186 (1973) [*CA* **86**, 89542 (1977)].

⁹⁵⁵ L. Kaczmarek, A. Becalski, and P. Nantka-Namirski, *Pol. J. Chem.* **54**, 1585 (1980).

⁹⁵⁶ F. M. Saidova, V. Binckauskas, S. G. Khorev, and E. Y. Enikeev, *Zh. Org. Khim.* **17**, 413 (1981).

⁹⁵⁷ Sterling Drug Inc., Netherlands Patent 06,511 (1980) [*CA* **95**, 187082 (1981)].

6. 4,4'-Bipyridine

a. *Quaternary Salts.* Various monoquaternary salts of 4,4'-bipyridines have been obtained by quaternization of 4,4'-bipyridines with one mole of an alkyl halide or other alkylating agent.^{91,949,958-962} The kinetics of the methylation of 4,4'-bipyridine with trimethyl phosphate have been investigated.⁹⁶¹ The sterically hindered 2,6-diphenyl-4,4'-bipyridine is preferentially methylated with methyl iodide on the 4'-nitrogen,⁷²⁵ and 1-benzyl-2,6-diphenyl-4,4'-bipyridinium tetrafluoroborate has interestingly been prepared by reaction of 2,6-diphenyl-4-(4-pyridyl)pyrylium salts with benzylamine.⁷²⁵ Several reactions of the monoquaternary salts have been studied. 1-Methyl-4,4'-bipyridinium iodide is preferentially hydrogenated in the quaternized ring to afford 1-methyl-4-(4-pyridyl)piperidine with a platinum oxide catalyst.⁹⁶³ The 1-alkyl monoquaternary salts are oxidized by alkaline ferricyanide to the corresponding bipyridin-2-one, further reactions of which have been studied.⁹⁶⁰ They also form charge-transfer complexes with electron donors.⁹⁶⁴ The polarographic behavior of the 1-methyl-4,4'-bipyridinium cation has been studied in aqueous solution,³⁷⁹ and its apparent dissociation constant in the presence of polyelectrolytes has been investigated.⁹⁶⁵ Cyanine dyes have been prepared from 1,2,2'-trimethyl-4,4'-bipyridinium iodide and related salts by condensation of the reactive 2-methyl group with 4-nitrosodimethylaniline, and similar condensations were described.⁹⁵⁹ 1-Cyano-4,4'-bipyridinium bromide is obtained by reaction of 4,4'-bipyridine with BrCN.⁹⁶⁶

There has been much interest in diquaternary salts of 4,4'-bipyridine, the electrochemistry of which has recently been reviewed.³⁸⁹ 1,1'-Dialkyl diquaternary salts of 4,4'-bipyridines are prepared by treating 4,4'-bipyridines with excess of an alkyl halide or a dialkyl sulfate or other alkylating agent. This method has been used extensively and provides diquaternary salts of type **92** where both alkyl quaternizing groups are the same (i.e., **92**: R = R').^{102,211,467,689,962,967,968} Of particular interest is the diquater-

⁹⁵⁸ B. Emmert and J. Stawitz, *Ber. Dtsch. Chem. Ges. B* **56**, 83 (1923).

⁹⁵⁹ A. B. Lal and V. Petrow, *J. Chem. Soc.*, S115 (1949).

⁹⁶⁰ S. Sugawara and N. Saito, *J. Pharm. Soc. Jpn.* **68**, 96 (1948).

⁹⁶¹ N. G. Sheremet, A. F. Vasil'ev, B. A. Khaskin, and N. N. Mel'nikov, *Zh. Obshch. Khim.* **43**, 2735 (1973).

⁹⁶² J. H. Ross and R. I. Krieger, *J. Agric. Food Chem.* **28**, 1026 (1980).

⁹⁶³ O. Johansen, A. Launikonis, J. W. Loder, A. W. H. Mau, W. H. F. Sasse, J. D. Swift, and D. Wells, *Aust. J. Chem.* **34**, 981 (1981).

⁹⁶⁴ V. Kampers and O. Neilands, *Zh. Obshch. Khim.* **47**, 442 (1977).

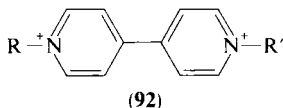
⁹⁶⁵ T. Shimidzu, J. Minamizono, Y. Akai, and H. Chiba, *J. Chem. Res., Synop.*, 348 (1979).

⁹⁶⁶ W. Konig, G. Ebert, and K. Centner, *Ber. Dtsch. Chem. Ges. B* **56**, 751 (1923).

⁹⁶⁷ S. Hunig and W. Schenk, *Justus Liebigs Ann. Chem.*, 727 (1979).

⁹⁶⁸ R. D. Balanson, M. E. Oxsen, and Y. Y. Cheng, *J. C. S. Perkin I*, 2704 (1979).

nary salt paraquat dichloride (**92**: $R = R' = \text{CH}_3$, $X = \text{Cl}$), which is an important herbicide, and several variations on this general method have been applied to its synthesis and to the syntheses of related herbicidal salts.⁴⁶⁷ Radioactive labeled paraquat has also been prepared by this route.^{841,969,970} In related syntheses, vinyl compounds such as acrylamide react with 4,4'-bipyridine in the presence of acid to afford diquaternary salts (e.g., **92**: $R = R' = \text{CH}_2\text{CH}_2\text{CONH}_2$).^{971,972} The kinetics of the methylation of 4,4'-bipyridine to the 1,1'-dimethyl-4,4'-bipyridinium dication with trimethyl phosphate have been studied.⁹⁶¹ Diquaternary salts of 4,4'-bipyridine, in which the alkyl quaternizing groups R and R' are different, have also been synthesized. They are usually obtained by treating a 1-alkyl monoquaternary salt with an excess of a different alkyl halide.^{467,725,962,973-976} Simple 1,1'-diphenyl diquaternary salts of 4,4'-bipyridines (e.g., **92**: $R = R' = \text{Ph}$) have not been prepared directly from 4,4'-bipyridines, using aryl halides, because of the low reactivity of the halogen atom in halobenzenes. However, the chloro group in 1-chloro-2,4-dinitrobenzene is active enough to react with 4,4'-bipyridine to afford 1,1'-bis(2,4-dinitrophenyl)-4,4'-bipyridinium dichloride [**92**: $R = R' = \text{C}_6\text{H}_3(\text{NO}_2)_2$]. This salt reacts with aniline to form 1,1'-diphenyl-4,4'-bipyridinium salts, and substituted anilines behave similarly. This reaction, therefore, serves as a means of preparing 1,1'-diaryl diquaternary salts of 4,4'-bipyridines.⁹⁷⁷⁻⁹⁸¹ 1,1'-Diaryl-4,4'-bipyridinium salts are also formed from the reaction of 4,4'-bipyridine with BrCN and anilines.⁹⁶⁶



⁹⁶⁹ P. Slade, *Weed Res.* **6**, 158 (1966).

⁹⁷⁰ A. J. Palmer, *J. Labelled Compd. Radiopharm.* **14**, 27 (1978).

⁹⁷¹ A. Le Berre and A. Delacroix, *Bull. Soc. Chim. Fr.*, 640 (1973).

⁹⁷² A. Le Berre and A. Delacroix, *Bull. Soc. Chim. Fr.*, 2404 (1973).

⁹⁷³ M. Okawara, T. Hirose, and N. Kamiya, *J. Polym. Sci., Polym. Chem. Ed.* **17**, 927 (1979).

⁹⁷⁴ H. Kamogawa, H. Mizuno, Y. Todo, and M. Nanasawa, *J. Polym. Sci., Polym. Chem. Ed.* **17**, 3149 (1979).

⁹⁷⁵ P. Tundo, K. Kurihara, D. J. Kippenberger, M. Politi, and J. H. Fendler, *Angew. Chem.* **94**, 73 (1982).

⁹⁷⁶ Hitachi, Ltd., Japanese Patent 110,778 (1981) [*CA* **96**, 113522 (1982)].

⁹⁷⁷ B. Emmert and N. Roh, *Ber. Dtsch. Chem. Ges. B* **58**, 503 (1925).

⁹⁷⁸ G. D. Short and L. Thomas, British Patent 1,310,813 (1973) [*CA* **78**, 159439 (1973)].

⁹⁷⁹ J. G. Allen, British Patent 1,399,595 (1975) [*CA* **83**, 147399 (1975)].

⁹⁸⁰ J. G. Allen, German Patent 2,527,638 (1976) [*CA* **85**, 78014 (1976)].

⁹⁸¹ G. P. Klimisha, I. P. Krainov, E. G. Protsenko, and B. G. Distanov, *Khim. Geterotsikl. Soedin.*, 264 (1979).

A number of other routes are available for the syntheses of diquaternary salts of 4,4'-bipyridines. One method that has been extensively studied involves reaction of a 1-alkylpyridinium salt with sodium amalgam (or sodium in liquid ammonia) to form the 1,1'-dialkyl-1,1',4,4'-tetrahydrobipyridine, which is readily oxidized to the corresponding 1,1'-dialkyl diquaternary salt. This reaction is analogous to the synthesis of 4,4'-bipyridine by the action of sodium on pyridine, followed by oxidation of the intermediate tetrahydrobipyridine.^{467,982-990} The reduction may be achieved electrolytically^{467,991-995} or by reaction with zinc or magnesium.⁹⁹⁶ Various oxidizing agents have been used to assist the conversion to the diquaternary salt.^{467,982,983,987} Another synthesis of diquaternary salts of 4,4'-bipyridines involving coupling of two pyridine rings consists of treating 1-methyl-4-cyanopyridinium iodide (**93**) with alkaline sodium dithionite whereby the radical cation of paraquat (**94**) is formed. The radical cation is readily oxidized to paraquat (**95**).⁹⁹⁷ Various extensions of this reaction, including studies of the mechanism of the reaction, have subsequently been reported.^{467,997-999} In a related synthesis, 1-alkylpyridinium salts couple in the presence of sodium cyanide to afford 1,1'-dialkyl-4,4'-bipyridinium diquaternary salts via the radical cation intermediate analogous to **94**.^{467,729,739,1000-1002} Phosphite or phosphinite ions may replace the

⁹⁸² B. Emmert and P. Parr, *Ber. Dtsch. Chem. Ges. B* **54**, 3168 (1921).

⁹⁸³ E. Weitz and R. Ludwig, *Ber. Dtsch. Chem. Ges. B* **55**, 395 (1922).

⁹⁸⁴ B. Emmert and O. Varenkamp, *Ber. Dtsch. Chem. Ges. B* **55**, 2322 (1922).

⁹⁸⁵ B. Emmert and O. Varenkamp, *Ber. Dtsch. Chem. Ges. B* **56**, 491 (1923).

⁹⁸⁶ E. Weitz and T. König, *Ber. Dtsch. Chem. Ges. B* **55**, 2864 (1922).

⁹⁸⁷ E. Weitz, T. König, and L. V. Wistinghausen, *Ber. Dtsch. Chem. Ges. B* **57**, 153 (1924).

⁹⁸⁸ B. Emmert, *Ber. Dtsch. Chem. Ges. B* **52**, 1351 (1919).

⁹⁸⁹ J. E. Colchester and J. H. Entwistle, British Patent 1,077,367 (1967) [*CA* **68**, 87175 (1968)]; British Patent, 1,073,082 (1967) [*CA* **69**, 59111 (1968)].

⁹⁹⁰ J. E. Colchester, British Patent 1,189,084 (1970) [*CA* **73**, 25315 (1970)].

⁹⁹¹ R. Raghavan and R. T. Iwamoto, *J. Electroanal. Chem. Interfacial Electrochem.* **92**, 101 (1978).

⁹⁹² T. Misumi, S. Furuhashi, and M. Shiga, German Patent, 2,812,508 (1978) [*CA* **90**, 22828 (1979)].

⁹⁹³ T. Misumi, Y. Usubuchi, and K. Kawai, Japanese Patent 135,985 (1978) [*CA* **90**, 186801 (1979)].

⁹⁹⁴ R. Raghavan and R. T. Iwamoto, *J. Electroanal. Chem. Interfacial Electrochem.* **102**, 85 (1979).

⁹⁹⁵ R. J. Gale and R. A. Osteryoung, *J. Electrochem. Soc.* **127**, 2167 (1980).

⁹⁹⁶ M. Onishi and S. Fujii, Japanese Patent 12,091 (1975) [*CA* **83**, 114214 (1975)]; Japanese Patent 12,090 (1975) [*CA* **83**, 114213 (1975)].

⁹⁹⁷ E. M. Kosower and J. L. Cotter, *J. Am. Chem. Soc.* **86**, 5524 (1964).

⁹⁹⁸ L. Grossi, F. Minisci, and G. F. Pedulli, *J. C. S. Perkin II*, 943 (1977).

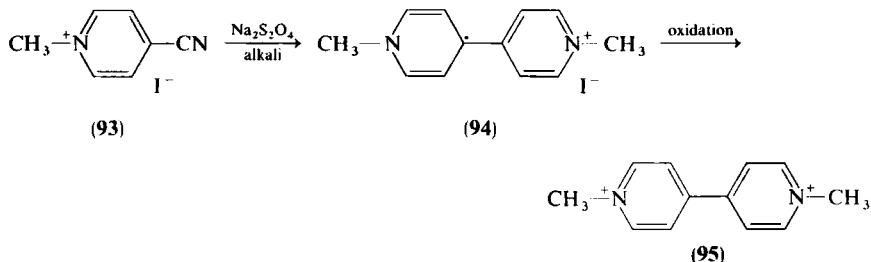
⁹⁹⁹ J. G. Carey and J. R. Case, *J. C. S. Perkin I*, 2431 (1977).

¹⁰⁰⁰ L. J. Winters, A. L. Borror, and N. Smith, *Tetrahedron Lett.*, 2313 (1967).

¹⁰⁰¹ Drexel Institute of Technology, German Patent 1,921,957 (1969) [*CA* **72**, 55264 (1970)].

¹⁰⁰² L. J. Winters, N. G. Smith, and M. I. Cohen, *J. C. S. Chem. Commun.*, 642 (1970).

cyanide in the reaction,¹⁰⁰³ and other anions may also be used.⁹⁹⁹ In an interesting reaction, the dimethiodide of di-4-pyridyl ketone and related monoquaternary salts rearrange to the radical cation of paraquat (94) in the presence of aqueous sodium hydroxide, and oxidation of 94 then affords a synthesis of paraquat (95). The mechanism of the reaction has been discussed.¹⁰⁰⁴⁻¹⁰⁰⁶



The diquaternary salts of 4,4'-bipyridine are strong electrolytes and are completely dissociated in water.¹⁰⁰⁷ Thermodynamic and viscosity measurements for solutions of paraquat dichloride in water have been obtained,^{1008,1009} and enthalpy data have been determined.¹⁰¹⁰ Distribution of the positive charges in the paraquat dication has been calculated from a quantum mechanical procedure.⁸⁵¹ There has been much interest in the spectra of diquaternary salts of 4,4'-bipyridine; UV,^{102,211,737-739,962,1011-1013} IR,^{739,854,1014,1015} Raman,¹⁰¹⁵⁻¹⁰¹⁷ proton NMR,^{211,737,739,813,855,962,1013} ^{13}C NMR,¹⁰¹⁸ and various mass spectra^{857-859,1019,1020} have all received some attention. High resolution X-ray diffraction analysis of

¹⁰⁰³ J. G. Carey and J. R. Case, *J. C. S. Perkin I*, 2429 (1977).

¹⁰⁰⁴ F. E. Geiger, C. L. Trichilo, F. L. Minn, and N. Filipescu, *J. Org. Chem.* **36**, 357 (1971).

¹⁰⁰⁵ R. B. Greenwald, U.S. Patent 3,772,026 (1973) [*CA* **80**, 114760 (1974)].

¹⁰⁰⁶ M. Frangopol, P. T. Frangopol, C. L. Trichilo, F. E. Geiger, and N. Filipescu, *J. Org. Chem.* **38**, 2355 (1974).

¹⁰⁰⁷ H. T. Van Dam, *J. Electrochem. Soc.* **123**, 1181 (1976).

¹⁰⁰⁸ R. F. Platford, *Environ. Sci. Technol.* **4**, 410 (1970).

¹⁰⁰⁹ G. Perron and J. E. Desnoyers, *J. Solution Chem.* **1**, 537 (1972).

¹⁰¹⁰ H. A. Gundry, D. Harrop, and A. J. Head, *J. Chem. Thermodyn.* **10**, 203 (1978).

¹⁰¹¹ I. S. Shchegoleva, *Khim. Vys. Energ.* **6**, 380 (1972) [*CA* **78**, 78062 (1973)].

¹⁰¹² A. Nakahara and J. H. Wang, *J. Phys. Chem.* **67**, 496 (1963).

¹⁰¹³ R. Fielden and L. A. Summers, *Experientia* **30**, 843 (1974).

¹⁰¹⁴ I. G. Burns, M. H. B. Hayes, and M. Stacey, *Pestic. Sci.* **4**, 201 (1973).

¹⁰¹⁵ M. Forster, R. B. Girling, and R. E. Hester, *J. Raman Spectrosc.* **12**, 36 (1982).

¹⁰¹⁶ A. Benchenane, L. Bernard, and T. Theophanides, *J. Raman Spectrosc.* **2**, 543 (1974).

¹⁰¹⁷ P. C. Lee, K. Schmidt, S. Gordon, and D. Meisel, *Chem. Phys. Lett.* **80**, 242 (1981).

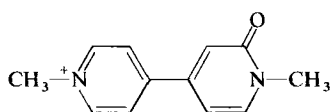
¹⁰¹⁸ J. E. Figard, J. V. Puakstelis, E. F. Byrne, and J. D. Petersen, *J. Am. Chem. Soc.* **99**, 8417 (1977).

¹⁰¹⁹ C. N. McEwen, S. F. Layton, and S. K. Taylor, *Anal. Chem.* **49**, 922 (1977).

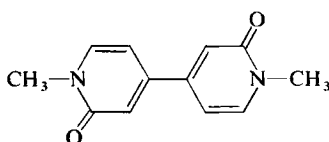
¹⁰²⁰ R. J. Day, S. E. Ungar, and R. G. Cooks, *J. Am. Chem. Soc.* **101**, 501 (1979).

1,1'-dimethyl-4,4'-bipyridinium salts confirm, as expected, that the bipyridinium dication is planar with the two methyl groups in approximately the same plane,¹⁰²¹⁻¹⁰²⁵ whereas in 1,1'-dibenzyl-4,4'-bipyridinium diiodide the benzyl groups and the bipyridinium dication, which are each planar, make a dihedral angle of 108° with each other.¹⁰²⁶

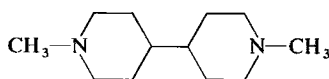
Several reactions of diquaternary salts of 4,4'-bipyridine have attracted attention. The behavior of 1,1'-dialkyl diquaternary salts in strong alkaline solution has long been of interest. They give intense blue-violet colorations on treatment with aqueous potassium hydroxide,^{982,1027,1028} and the deep color is discharged on shaking in air. The blue-violet color is largely due to radical cations such as **94**. The mechanism of the reaction of paraquat dication (**95**) with alkali has been elucidated. There are several competing reactions,^{813,1029,1030} but an important step involves demethylation of the paraquat dication to the 1-methyl-4,4'-bipyridinium cation under the influence of alkali with generation of methanol. This is followed by reaction of methoxide ion with the paraquat dication (**95**) to give the paraquat radical cation (**94**) and formaldehyde. As expected pyridones such as **96** and **97** are formed in competing reactions. In a 1979 patent, it is suggested that paraquat can be completely demethylated by strong alkali to afford some 4,4'-bipyridine.¹⁰³¹



(96)



(97)



(98)

¹⁰²¹ J. H. Russell and S. C. Wallwork, *Acta Crystallogr. Sect. B* **B28**, 1527 (1972).

¹⁰²² C. K. Prout and P. Murray-Rust, *J. Chem. Soc. A*, 1520 (1969).

¹⁰²³ J. H. Russell and S. C. Wallwork, *Acta Crystallogr., Sect. B* **B25**, 1691 (1969).

¹⁰²⁴ P. Murray-Rust, *Acta Crystallogr., Sect. B* **B31**, 1771 (1975).

¹⁰²⁵ S. S. Basson, L. D. C. Bok, and J. G. Leipoldt, *Acta Crystallogr., Sect. B* **B25**, 579 (1969).

¹⁰²⁶ J. H. Russell and S. C. Wallwork, *Acta Crystallogr., Sect. B* **B27**, 2473 (1971).

¹⁰²⁷ H. Weidel and M. Russo, *Monatsh. Chem.* **3**, 850 (1882).

¹⁰²⁸ B. Emmert and V. Dollein, *Ber. Dtsch. Chem. Ges.* **B** **56**, 2068 (1923).

¹⁰²⁹ A. H. Corwin, R. R. Arellano, and A. B. Chivvis, *Biochim. Biophys. Acta* **162**, 533 (1968).

¹⁰³⁰ J. A. Farrington, A. Ledwith, and M. F. Stam, *J. C. S. Chem. Commun.*, 259 (1969).

¹⁰³¹ T. D. Bailey and C. K. McGill, U.S. Patent 4,158,093 (1979) [*CA* **91**, 123636 (1979)].

Catalytic hydrogenation of 1,1'-dialkyl diquaternary salts of 4,4'-bipyridine affords fully reduced bipiperidine derivatives such as **98**,^{764,765,822,866,867} although controlled hydrogenation results in reduction of one ring only.^{845,963} Reduction with sodium borohydride gives partly reduced derivatives,^{868,869} although sodium borohydride with a metal catalyst, such as nickel chloride, affords fully reduced species.¹⁰³² As was the case with diquaternary salts of 2,2'-bipyridine, reduction of 1,1'-dialkyl diquaternary salts of 4,4'-bipyridine, such as the paraquat dication (**95**), by one-electron reducing agents in aqueous solution gives rise to an intense violet coloration because of the stable radical cation **94**. The one-electron transfer is completely reversed by air. The radical cation **94** can take up another electron to form the neutral species **99**. The stability of the radical cation **94** is due to the ability of the odd electron to be located at any of the nuclear positions because of the coplanarity of the two pyridine rings. The early work on the one-electron reduction of diquaternary salts of 4,4'-bipyridine was carried out mainly by Weitz and his colleagues.^{467,983,986,1033} The reduced form **99** has been obtained pure.¹⁰³⁴ Reduction of the colorless diquaternary salts like **95** to the highly colored radical cations can occur in biological systems and consequently the diquaternary salts have been extensively used as redox indicators under the name *viologens*. The reduction potential E_0 of the first step with paraquat ($\mathbf{95} \rightleftharpoons \mathbf{94}$) occurs at -0.45 V in aqueous solution, and other 1,1'-dialkyl diquaternary salts of 4,4'-bipyridine are reduced at similar low potentials.^{1035,1036} The first reduction step is independent of pH because no hydrogen is involved. The second reduction step ($\mathbf{94} \rightleftharpoons \mathbf{99}$), which is readily measured by polarography is usually pH dependent presumably because of protonation of the radical cation. In the case of paraquat it occurs at about -0.80 V at alkaline pH. The reduction potential in aqueous solution of numerous 1,1'-dialkyl diquaternary salts of 4,4'-bipyridines have subsequently been measured.^{389,467,845,968} Further polarography and voltammetry studies have been reported.^{882,1037-1041} Considerable work on the one-electron reduction in nonaqueous or mixed

¹⁰³² S. Ukai, K. Hirose, and S. Kawase, *Eisei Kagaku* **23**, 83 (1977).

¹⁰³³ E. Weitz, *Angew. Chem.* **66**, 658 (1954).

¹⁰³⁴ J. G. Carey, J. F. Cairns, and J. E. Colchester, *J. C. S. Chem. Commun.*, 1280 (1969).

¹⁰³⁵ L. Michaelis, *Biochem. Z.* **250**, 564 (1932).

¹⁰³⁶ L. Michaelis and E. S. Hill, *J. Gen. Physiol.* **16**, 859 (1933).

¹⁰³⁷ V. N. Grachev, S. I. Zhdanov, G. S. Supin, and B. A. Khaskin, *Zh. Anal. Khim.* **33**, 368 (1978).

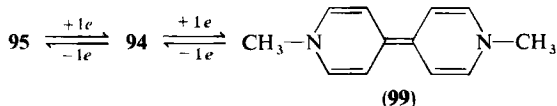
¹⁰³⁸ L. Pospisil and J. Kuta, *J. Electroanal. Chem. Interfacial Electrochem.* **90**, 231 (1978).

¹⁰³⁹ J. Bruinink and C. G. A. Kregting, *J. Electrochem. Soc.*, **125**, 1397 (1978).

¹⁰⁴⁰ V. N. Grachev, S. I. Zhdanov, and G. S. Supin, *Elektrokhimiya* **14**, 1353 (1978).

¹⁰⁴¹ V. N. Grachev and S. I. Zhdanov, *Elektrokhimiya* **15**, 1154 (1979).

solvent systems, mainly using polarography, has also been published.^{211,467,739,879,881,1042-1046} The one-electron reduction of 1,1'-dialkyl diquatery salts of 4,4'-bipyridine can be accomplished by means other than chemical reduction. The radical cations can be generated by irradiation,^{317,467,1011,1047} sometimes with the aid of sensitizers^{467,1048-1050} or in polymer matrices,^{1051,1052} electrochemically,⁴⁶⁷ by exposure to radiofrequency plasma,¹⁰⁵³ and by various enzymes and other biological systems, especially those connected with photosynthesis in plants.^{467,1054} Thermodynamic data have been calculated for the one-electron reduction of the viologens with several reducing agents.¹⁰⁵⁵



The spectra of the radical cations derived from 1,1'-dialkyl diquatery salts of 4,4'-bipyridine have received attention, the UV^{467,739,853,885,886,997,1029,1036,1056} and ESR spectra having been well studied.^{317,467,997,1057-1059} It is evident from some of these studies that the radical cations are in equilibrium with dimeric species.^{467,1046,1057,1059} The Raman spectra of paraquat and its radical cation adsorbed at a silver electrode have also been investigated,¹⁰⁶⁰ whereas a resonance Raman effect with radical cations of viologens has been noted.^{1015,1017,1061} Other Raman studies at metal

¹⁰⁴² V. I. Gavrilov, O. A. Ushakov, and I. V. Shelepin, *Elektrokhimiya* **14**, 1102 (1978).

¹⁰⁴³ V. F. Vargalyuk, T. I. Starokozheva, Y. M. Loshkarev, and N. Y. Savel'eva, *Elektrokhimiya* **15**, 238 (1979).

¹⁰⁴⁴ V. F. Vargalyuk, T. I. Starokozheva, and Y. M. Loshkarev, *Elektrokhimiya* **15**, 1551 (1979).

¹⁰⁴⁵ S. Hunig and W. Schenk, *Justus Liebigs Ann. Chem.*, 1523 (1979).

¹⁰⁴⁶ M. Mohammad, R. Iqbal, A. Y. Khan, M. Bhatti, K. Zahir, and R. Jahan, *J. Phys. Chem.* **85**, 2816 (1981).

¹⁰⁴⁷ T. W. Ebbesen, G. Levey, and L. K. Patterson, *Nature (London)* **298**, 545 (1982).

¹⁰⁴⁸ F. D. Saeva, G. R. Olin, and J. R. Harbour, *J. C. S. Chem. Commun.*, 410 (1980).

¹⁰⁴⁹ J. R. Darwent, *J. C. S. Chem. Commun.*, 805 (1980).

¹⁰⁵⁰ M. Kaneko and A. Yamada, *Photochem. Photobiol.* **33**, 793 (1981).

¹⁰⁵¹ H. Kamogawa, T. Masui, and M. Nanasawa, *Chem. Lett.*, 1145 (1980).

¹⁰⁵² M. Kaneko and A. Yamada, *Makromol. Chem.* **182**, 1111 (1981).

¹⁰⁵³ Y. Osada and Y. Iriyama, *J. Am. Chem. Soc.* **104**, 2925 (1982).

¹⁰⁵⁴ T. Endo and M. Okawara, *J. Org. Chem.* **45**, 2663 (1980).

¹⁰⁵⁵ G. D. Watt and A. Burns, *Biochem. J.* **152**, 33 (1975).

¹⁰⁵⁶ T. Watanabe and K. Honda, *J. Phys. Chem.* **86**, 2617 (1982).

¹⁰⁵⁷ A. G. Evans, J. C. Evans, and M. W. Baker, *J. Am. Chem. Soc.* **99**, 5882 (1977).

¹⁰⁵⁸ W. R. Durham, J. A. Fee, L. J. Harding, and H. J. Grande, *J. Magn. Reson.* **40**, 351 (1980).

¹⁰⁵⁹ J. C. Evans, M. H. N. Sorkhabi, and C. C. Rowlands, *Tetrahedron* **38**, 2581 (1982).

¹⁰⁶⁰ A. Regis and J. Corset, *J. Chim. Phys. Phys.-Chim. Biol.* **78**, 687 (1981).

¹⁰⁶¹ M. Forster and R. E. Hester, *Chem. Phys. Lett.* **85**, 287 (1982).

electrodes confirm that viologen radical cations are in equilibrium with dimeric species.¹⁰⁶²

The kinetics of the electron transfer between 1,1'-dialkyl diquatary salts of 4,4'-bipyridine and their radical cations have been studied.¹⁰⁶³ The rate constants for the one-electron reduction of paraquat and related salts have been determined by pulse radiolysis. The constants are extremely large, a value of $8 \times 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$ being typical for the reduction of paraquat in water.^{886,1064-1069} Other kinetic studies on various electron transfer reactions involving the viologen radical cations have been reported,^{467,886,1070} including some reactions at hydrogen-evolving metal electrodes.⁸⁹⁰ Long-chain alkyl viologens, such as 1-ethyl-1'-cetyl-4,4'-bipyridinium dibromide, form micelles in aqueous solution, and the rate of electron exchange with its radical cation on the micellar surface has been studied by ESR spectroscopy.¹⁰⁷¹ As was the case with the diquat radical cation, considerable attention has been paid to the reaction of viologen radical cations, especially the paraquat radical cation (**94**) with oxygen. In the oxidation of **94** back to the paraquat diquatary salt (**95**), oxygen is converted to the superoxide radical anion, O_2^- .^{467,887,1046,1064-1066,1072-1074} This work has been extended to include the kinetics of the reaction of **99** as well as **94** with oxygen and also the rate of protonation of these species.¹⁰⁴⁶ The pK for the protonation of **94** has been determined as 2.9.¹⁰⁶⁹ The oxidation of **94** with several peroxides⁸⁹⁵ and quinones¹⁰⁷⁵ has also been studied. Interestingly, the paraquat radical cation gives hydrogen gas in the presence of hydrogen ions and platinum black¹⁰⁷⁶ and other metal catalysts.¹⁰⁷⁷ The reaction of

¹⁰⁶² M. Ohsawa, K. Nishijima, and W. Suetaka, *Surf. Sci.* **104**, 270 (1981).

¹⁰⁶³ N. Winograd and T. Kuwana, *J. Am. Chem. Soc.* **92**, 224 (1970).

¹⁰⁶⁴ J. A. Farrington, M. Ebert, E. J. Land, and K. Fletcher, *Biochim. Biophys. Acta* **314**, 372 (1973).

¹⁰⁶⁵ J. A. Farrington, M. Ebert, and E. J. Land, *J. C. S. Faraday I* **74**, 665 (1978).

¹⁰⁶⁶ L. K. Patterson, R. D. Small, and J. C. Scaiano, *Radiat. Res.* **72**, 218 (1977).

¹⁰⁶⁷ M. A. J. Rodgers, D. C. Foyt, and Z. A. Zimek, *Radiat. Res.* **75**, 296 (1978).

¹⁰⁶⁸ Y. N. Kozlov, Y. E. Kats, B. A. Kiselev, and V. B. Evstigneev, *Biofizika* **24**, 583 (1979).

¹⁰⁶⁹ S. Solar, W. Solar, N. Getoff, J. Holcman, and K. Sehested, *J. C. S. Faraday I*, **78**, 2467 (1982).

¹⁰⁷⁰ W. Boettcher and A. Haim, *Inorg. Chem.* **21**, 531 (1982).

¹⁰⁷¹ K. Takuma, T. Sakamoto, T. Nagamura, and T. Matsuo, *J. Phys. Chem.* **85**, 619 (1981).

¹⁰⁷² A. G. Evans, R. E. Alford, and N. H. Rees, *J. C. S. Perkin II*, 1831 (1975).

¹⁰⁷³ A. G. Evans, N. K. Dodson, and N. H. Rees, *J. C. S. Perkin II*, 859 (1976).

¹⁰⁷⁴ E. F. Elstner, H. P. Fischer, W. Osswald, and G. Kwiatkowski, *Z. Naturforsch., C: Biosci.* **35C**, 770 (1980).

¹⁰⁷⁵ J. R. Darwent and K. Kalyanasundaram, *J. C. S. Faraday II* **77**, 373 (1981).

¹⁰⁷⁶ M. Kaneko, H. Araki and A. Yamada, *Sci. Pap. Inst. Phys. Chem. Res. (Jpn.)* **73**, 67 (1979) [*CA* **92**, 197570 (1980)].

¹⁰⁷⁷ D. S. Miller, A. J. Bard, G. McLendon, and J. Ferguson, *J. Am. Chem. Soc.* **103**, 5336 (1981).

the paraquat dication with hydrogen atoms has been studied by pulse radiolysis. Several reactions are involved, including attack of hydrogen on the pyridine rings and formation of the protonated form of the paraquat radical cation.¹⁰⁶⁹

The oxidation of 1,1'-dialkyl diquaternary salts of 4,4'-bipyridine has also been studied. With potassium ferricyanide they give bipyridinones of types **96** and **97**.^{813,960} Similar results were obtained on air oxidation of paraquat at 80°C.¹⁰⁷⁸ Pyrolysis of paraquat results in demethylation to 4,4'-bipyridine, and this reaction forms the basis of a gas chromatographic method of analysis of the compound.^{1079,1080} Diquat behaves similarly. 1,1'-Dialkyl diquaternary salts of 4,4'-bipyridines are electron acceptors, and they form complexes with many electron-donor molecules including various amines and phenols,^{467,1081} biologically important molecules,⁴⁶⁷ various anions,^{467,854,855,1012,1082,1083} and 7,7,8,8-tetracyanoquinodimethane. Some of the latter complexes show low electrical resistivity and are of interest as electrical conductors.^{467,1084} The paraquat-*p*-phenylenediamine complex on flash photolysis yields the paraquat radical cation and the *p*-phenylenediamine radical cation by electron transfer.¹⁰⁸⁵ The complexes between paraquat and surfactant stilbenes have been used in studies of hydrophobic-hydrophilic interactions in sodium dodecyl sulfate micelles.^{1086,1087} The high resolution X-ray diffraction analyses of several of these complexes have been reported.^{467,1021,1022,1088-1091} A few other reactions of 1,1'-dialkyl diquaternary salts of 4,4'-bipyridine deserve mention. Paraquat on irradiation in aqueous solution can act as an oxidizing agent for converting primary and secondary alcohols to the corresponding carbonyl compounds. In the process paraquat is reduced to its radical cation. An important step in the mechanism to account for the reaction is the oxidation of alcohols to alkoxy radicals by singlet-excited paraquat.⁸⁹⁹ Considerable further work on the

¹⁰⁷⁸ M. Forster and R. E. Hester, *J. C. S. Faraday I*, **78**, 1847 (1982).

¹⁰⁷⁹ M. A. Martens and A. Heyndrickx, *J. Pharm. Belg.* **29**, 444 (1974).

¹⁰⁸⁰ J. A. Beutler, A. Varano, and A. Der Marderosian, *J. Forensic Sci.* **24**, 808 (1979).

¹⁰⁸¹ A. S. N. Murthy and A. P. Bhardwaj, *Spectrochim. Acta, Part A* **38A**, 207 (1982).

¹⁰⁸² J. C. Curtis, B. P. Sullivan and T. J. Meyer, *Inorg. Chem.* **19**, 3833 (1980).

¹⁰⁸³ A. Deronzier, *J. C. S. Chem. Commun.*, 329 (1982).

¹⁰⁸⁴ D. D. Eley, G. J. Ashwell, S. C. Wallwork, M. R. Willis, and J. Woodward, *Ann. N.Y. Acad. Sci.* **313**, 417 (1978).

¹⁰⁸⁵ A. T. Poulas, C. K. Kelley, and R. Simone, *J. Phys. Chem.* **85**, 823 (1981).

¹⁰⁸⁶ J. C. Russell, D. G. Whitten, and A. M. Braun, *J. Am. Chem. Soc.* **103**, 3219 (1981).

¹⁰⁸⁷ F. M. Martens and J. W. Verhoeven, *J. Phys. Chem.* **85**, 1773 (1981).

¹⁰⁸⁸ G. J. Ashwell, I. Diaconu, D. D. Eley, S. C. Wallwork, and M. R. Willis, *Z. Naturforsch., A* **34A**, 1 (1979).

¹⁰⁸⁹ G. J. Ashwell and S. C. Wallwork, *Acta Crystallogr., Sect. B* **B35**, 1648 (1979).

¹⁰⁹⁰ M. M. Mahmoud and S. C. Wallwork, *Acta Crystallogr., Sect. B* **B37**, 398 (1981).

¹⁰⁹¹ K. Nakamura, Y. Kai, N. Yasuoka, and N. Kasai, *Bull. Chem. Soc. Jpn.* **54**, 3300 (1981).

mechanism has been reported.^{1076,1092-1097} Anions such as formate, oxalate, and benzoate are also oxidized in aqueous solution by paraquat in photoinduced reactions.⁹⁰⁰ The 1,1'-di(4-pyridyl)-4,4'-bipyridinium dication is decomposed by hot aqueous acid to 4,4'-bipyridine and 4-pyridone.⁷²⁹

Tetraquatery salts have been prepared by treating 1-methyl-4,4'-bipyridinium salts with, for example, *N,N'*-(β -bromoethyl)dicarboxamides, and their reduction to radical cations has been investigated as components of redox membranes and vesicles.¹⁰⁹⁸ Other work on the reduction of tetraquatery salts to radical cations has been reported.^{1099,1100} Polyviologens have also been synthesized, for example, by treating 4,4'-bipyridine with α,α' -dibromoxylenes, dichloromethane, or 1,10-dibromodecane, and their photochromic, electrical conductivity, and redox properties have been studied.^{467,973,974,1101-1110}

Quatery salts of 4,4'-bipyridine other than 1-alkyl or 1-aryl quatery salts have also been synthesized. Thus 1,1'-dialkoxy diquatery salts are formed by reaction of 4,4'-bipyridine 1,1'-dioxide (see next section) with dialkyl sulfates,¹¹¹¹ and 1-alkyl-1'-alkoxy diquatery salts are obtained similarly. 1,1'-Bis(2,4-dinitrophenoxy)-4,4'-bipyridinium bis(fluoroborate) has been prepared from 4,4'-bipyridine 1,1'-dioxide by reaction with 2,4-dinitrobenzenediazonium fluoroborate in sulfolane.¹¹¹² Interestingly,

¹⁰⁹² A. S. Hopkins and A. Ledwith, *J. C. S. Chem. Commun.*, 830 (1971).

¹⁰⁹³ N. M. D. Brown, D. J. Cowley, and W. J. Murphy, *J. C. S. Chem. Commun.*, 592 (1973).

¹⁰⁹⁴ N. M. D. Brown, D. J. Cowley, and W. J. Murphy, *J. C. S. Perkin II*, 1769 (1976).

¹⁰⁹⁵ P. Hyde and A. Ledwith, *J. C. S. Perkin II*, 1768 (1974).

¹⁰⁹⁶ N. M. D. Brown, D. J. Cowley, and M. Hashmi, *J. C. S. Perkin II*, 462 (1979).

¹⁰⁹⁷ M. A. J. Rodgers, *Photochem. Photobiol.* **29**, 1031 (1979).

¹⁰⁹⁸ E. Baumgartner and J. H. Fuhrhop, *Angew. Chem., Int. Ed. Engl.* **19**, 550 (1980).

¹⁰⁹⁹ M. Furue and S. Nozakura, *Chem. Lett.*, 821 (1980); *Bull. Chem. Soc. Jpn.* **55**, 513 (1982).

¹¹⁰⁰ A. Deronzier, B. Galland, and M. Vieira, *Nouv. J. Chim.* **6**, 97 (1982).

¹¹⁰¹ M. S. Simon, U.S. Patent 3,641,034 (1972) [*CA* **77**, 6022 (1972)].

¹¹⁰² A. Factor and G. E. Heinsohn, U.S. Patent 3,694,384 (1972) [*CA* **77**, 165534 (1972)].

¹¹⁰³ K. Sanada, A. Iwasawa, E. Tsuchida, and I. Shinohara, *Nippon Kagaku Kaishi*, 961 (1974).

¹¹⁰⁴ V. A. Kabanov, K. V. Aliev, and J. Richmond, *J. Appl. Polym. Sci.* **19**, 1275 (1975).

¹¹⁰⁵ A. A. Ziyaev, O. S. Otroshchenko, A. S. Sadykov, G. A. Tolкачева, and K. D. Khalilova, U.S.S.R. Patent 476,257 (1975) [*CA* **83**, 132295 (1975)].

¹¹⁰⁶ T. Muramatsu, K. Nagayasu, M. Kimura, S. Terada, and M. Mayama, Japanese Patent 42,535 (1976) [*CA* **85**, 134293 (1976)].

¹¹⁰⁷ M. Okawara, T. Endo, E. Fujiwara, and T. Hirose, *J. Macromol. Sci., Chem.* **A13**, 441 (1979).

¹¹⁰⁸ R. B. Cundall, J. B. Lawton, D. Murray, and G. O. Phillips, *Makromol. Chem.* **180**, 2913 (1979).

¹¹⁰⁹ Y. A. Aleksandrovskii, A. A. Sukhno, and Y. V. Rodionov, *Biokhimiya (Moscow)* **44**, 2130 (1979).

¹¹¹⁰ L. M. Mukherjee and B. B. Prasad, *J. Macromol. Sci., Chem.* **A16**, 1263 (1981).

¹¹¹¹ R. Fielden and L. A. Summers, *J. Heterocycl. Chem.* **11**, 299 (1974).

¹¹¹² R. A. Abramovitch, M. N. Inbasekaran, S. Kato, and G. M. Singer, *J. Org. Chem.* **41**, 1717 (1976).

this diquaternary salt decomposes in boiling water to 2,4-dinitrophenol and 4,4'-bipyridin-2,2'-dione. Unlike 1,1'-dialkyl diquaternary salts of 4,4'-bipyridine, 1,1'-dialkoxy, and 1-alkyl-1'-alkoxy diquaternary salts cannot be regarded as the oxidized forms of reversible redox systems. They are broken down in aqueous solution on treatment with a reducing agent such as zinc dust, and their polarographic behavior is complex.^{389,1045,1111} 1,1'-Dimethoxy-4,4'-bipyridinium bis(methylsulfate) reacts with potassium cyanide to afford 2,2'-dicyano-4,4'-bipyridine.¹⁰¹³ 1-Amino- and 1,1'-diamino-4,4'-bipyridinium salts have also been prepared from the reaction of 4,4'-bipyridine with hydroxylamine-*O*-sulfonic acid^{1113,1114} or *O*-mesitylene-sulfonylhydroxylamine.⁹⁰¹ In another route to compounds of this type, 1-(dimethylamino)-4,4'-bipyridinium salts are formed by treatment of 1-(2,4-dinitrophenyl)-4,4'-bipyridinium salts with *N,N*-dimethylhydrazine.⁹⁶⁷ 1,1'-Diamino-4,4'-bipyridinium salts do not give stable radical cations on reduction in aqueous solution, and their polarographic waves are complicated.¹¹¹³ The polarography of salts of this type in nonaqueous solvents has also been investigated.¹⁰⁴⁵ In dilute alkali they give a deep red coloration possibly because of the loss of a proton and formation of a nitrogen betaine,¹¹¹³ whereas with acyl chlorides, such as benzoyl chloride, other betaines are obtained.^{901,939} Similarly, 1,1'-diamino-4,4'-bipyridinium dinitrate is dehydrated by trifluoroacetic anhydride to the bis-*N*-nitroimide.¹¹¹⁵ To conclude the section on the synthesis of quaternary salts of 4,4'-bipyridine, we note the formation of bis(methylsulfato) betaines by reaction of 4,4'-bipyridine with sulfur trioxide and paraformaldehyde,¹¹¹⁶ the synthesis of related sulfatobetaines, using ethylenesulfonyl chloride,¹¹¹⁷ and other reagents,¹¹¹⁸ and the synthesis and polarography studies of various C-ylides of 4,4'-bipyridine formed by reaction of 4,4'-bipyridine with diethyl bromomalonate and related compounds.^{967,1045}

b. *N*-Oxides. As with the other bipyridines, 4,4'-bipyridine reacts with hydrogen peroxide in glacial acetic acid to afford the 1-oxide or 1,1'-dioxide, depending on conditions.¹¹¹¹ The 1,1'-dioxide is also formed, using *tert*-amyl hydroperoxide,¹¹¹⁹ and the 1-oxides of substituted 4,4'-bipyridines

¹¹¹³ J. E. Downes, *J. Chem. Soc. C*, 2192 (1967).

¹¹¹⁴ J. E. Downes, British Patent 1,108,174 (1968) [*CA* **69**, 67229 (1968)].

¹¹¹⁵ J. Epszajn, A. R. Katritzky, E. Lunt, J. W. Mitchell, and G. Roch, *J. C. S. Perkin I*, 2622 (1973).

¹¹¹⁶ D. L. Klass, U.S. Patent 3,320,266 (1967) [*CA* **67**, 100010 (1967)].

¹¹¹⁷ A. Le Berre, A. Etienne, and B. Dumaitre, *Bull. Soc. Chim. Fr.*, 954 (1970).

¹¹¹⁸ P. A. Brugger, M. Gratzel, T. Guarr, and G. McLendon, *J. Phys. Chem.* **86**, 944 (1982).

¹¹¹⁹ G. A. Tolstikov, U. M. Jemilev, V. P. Jurjev, F. B. Gershanov, and S. R. Rafikov, *Tetrahedron Lett.*, 2807 (1971).

have been obtained, using perbenzoic acid¹¹²⁰ or hydrogen peroxide in sulfuric-trifluoroacetic acid mixtures.¹¹²¹ The *N*-oxides are converted back to 4,4'-bipyridine by a variety of reagents^{910,1120} and may be used as dehydrogenating agents.⁹¹¹ The IR,^{912,916,917,1122} UV,^{917,924} photoelectron,¹⁵¹ proton NMR,⁹¹⁸⁻⁹²⁰ and ¹³C NMR spectra have all been investigated,^{921,922} and their polarographic reduction has been studied.⁹²⁵ Attempts to nitrate the *N*-oxides result in deoxygenation instead of nitration,¹¹²³ and bromination attempts gave similar results.⁹⁴⁴

E. METAL COMPLEXES OF 2,2'-BIPYRIDINE

The ability of 2,2'-bipyridine and its derivatives to form complexes with metals and nonmetals is well known, and the subject has been thoroughly reviewed.^{324,1124-1135} Further discussion of this topic is outside the scope of this review.

F. REACTIONS OF SUBSTITUTED BIPYRIDINES

1. 2,2'-Bipyridine

Several standard reactions have been applied to substituents in 2,2'-bipyridines. Methyl-substituted 2,2'-bipyridines are oxidized to the corresponding carboxylic acids by permanganate^{416,470,928,1136,1137} or by

¹¹²⁰ B. M. Bain and J. E. Saxton, *J. Chem. Soc.*, 5216 (1961).

¹¹²¹ G. E. Chivers and H. Suschitzky, *J. Chem. Soc. C*, 2867 (1971).

¹¹²² V. P. Gupta, *Indian J. Pure Appl. Phys.* **7**, 423 (1969).

¹¹²³ Y. V. Kurbatov, V. S. Tsukervanik, O. S. Otroshchenko, and A. S. Sadykov, *Tr. Samark. Gos. Univ. im. Alishera Navoi* **167**, 65 (1969) [*CA* **74**, 141475 (1971)].

¹¹²⁴ W. W. Brandt, F. P. Dwyer, and E. C. Gyarfas, *Chem. Rev.* **54**, 959 (1954).

¹¹²⁵ L. F. Lindoy and S. E. Livingstone, *Coord. Chem. Rev.* **2**, 173 (1967).

¹¹²⁶ R. Taube and S. Herzog, *Z. Chem.* **2**, 225 (1962).

¹¹²⁷ E. Konig, *Coord. Chem. Rev.* **3**, 471 (1968).

¹¹²⁸ F. P. Dwyer and D. P. Mellor, "Chelating Agents and Metal Chelates," Academic Press, New York, 1964.

¹¹²⁹ S. F. Mason, *Inorg. Chim. Acta, Rev.* **2**, 89 (1968).

¹¹³⁰ W. R. McWhinnie and J. D. Miller, *Adv. Inorg. Chem. Radiochem.* **12**, 135 (1969).

¹¹³¹ A. T. Pilipenko and E. R. Falendysh, *Usp. Khim.* **41**, 2094 (1972).

¹¹³² E. D. McKenzie, *Coord. Chem. Rev.* **6**, 187 (1971).

¹¹³³ H. Sigel, *Met. Ions Biol. Syst.* **2**, 63 (1973).

¹¹³⁴ R. D. Gillard, *Coord. Chem. Rev.* **16**, 67 (1975).

¹¹³⁵ C. Creutz, *Comments Inorg. Chem.* **1**, 293 (1982).

¹¹³⁶ C. P. Whittle, *J. Heterocycl. Chem.* **14**, 191 (1977).

¹¹³⁷ K. D. Bos, J. G. Kraaijkamp, and J. G. Noltes, *Synth. Commun.* **9**, 497 (1979).

selenium dioxide,^{408,826} although when the latter reagent is used, the intermediate aldehyde is sometimes isolated.^{826,1138} Oxidation of 5,5'-bis(1-methyl-2-piperidyl)-2,2'-bipyridine affords 2,2'-bipyridine-5,5'-dicarboxylic acid.⁴⁷⁴ 4,4'-Dimethyl-2,2'-bipyridine on treatment with sodamide in liquid ammonia, followed by reaction with an alkyl bromide, results in extension of the alkyl chain. Thus using hexyl bromide, 4,4'-diheptyl-2,2'-bipyridine was obtained,¹¹³⁷ whereas 4-methyl-2,2'-bipyridines have been converted to 4- β -hydroxyethyl derivatives via lithium reagents and formaldehyde and hence to 4-vinyl analogs by dehydration.⁴⁸⁵ Other chain extension reactions have been applied to 6-lithiomethyl-2,2'-bipyridine.¹¹³⁹ 4,4'-Dimethyl-2,2'-bipyridines, but not the 5,5'-dimethyl analogs, form distyryl-2,2'-bipyridines on reaction with benzaldehyde. The styryl groups were subsequently hydrogenated, using a palladium catalyst, to the corresponding phenylethyl substituents.⁴⁷⁰ The reaction proceeds too with thiophene-2-aldehydes. Subsequent hydrogenation with Raney nickel leads in this case to desulfurization, and this method therefore serves as another synthesis of 2,2'-bipyridines with long alkyl chain substituents in the 4,4'-positions.¹¹⁴⁰ Terephthalaldehyde condenses similarly with 4,4'-dimethyl-2,2'-bipyridine to give polymer precursors.¹¹⁴¹ Other work on the use of 2,2'-bipyridine aldehydes in polymerization reactions has been reported.⁵³⁸ Decarboxylation of 2,2'-bipyridine carboxylic acids has been performed on several occasions,^{96,403,404,407} whereas esterification of the carboxylic acids,^{416,470,928,1136,1137,1142} followed by conversion to amides^{928,1136} and subsequent Hofmann degradation to amino-2,2'-bipyridines, has been reported.⁹²⁸ The esters have been reduced by lithium aluminum hydride to the hydroxymethyl compounds and condensed with hydrazine to give hydrazides, which were converted to azides and then to amines by a Curtius rearrangement.¹¹³⁶ 3,3'-Bis(hydroxymethyl)-2,2'-bipyridine condenses with ditosylate derivatives of polyethylene glycols to give crown ethers of type **100**,^{1143,1144} and 3,3'-dihydroxy-2,2'-bipyridines behave likewise.⁵⁵⁰ The diacid chloride of 2,2'-bipyridine-6,6'-dicarboxylic acid reacts with a variety of long-chain diamines to give compounds such as **101**,¹¹⁴⁵ and the diacid

¹¹³⁸ M. Seyhan and W. C. Fernelius, *Chem. Ber.* **91**, 469 (1958).

¹¹³⁹ T. Kauffmann, J. Ennen, H. Lhotak, A. Rensing, F. Steinseifer, and A. Woltermann, *Angew. Chem., Int. Ed. Engl.* **19**, 328 (1980).

¹¹⁴⁰ O. Johansen, C. Kowala, A. W. H. Mau, and W. H. F. Sasse, *Aust. J. Chem.* **32**, 1453 (1979).

¹¹⁴¹ R. Chapurlat and E. Kuntz, German Patent 2,037,412 (1971) [*CA* **75**, 667 (1971)]; German Patent 2,049,057 (1971) [*CA* **75**, 21513 (1971)].

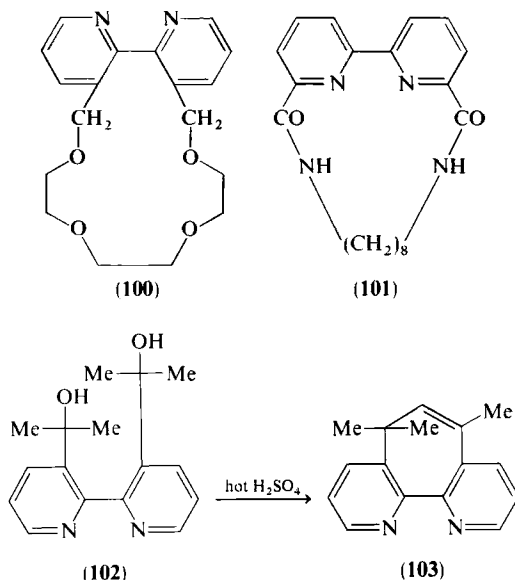
¹¹⁴² Y. N. Forostyan, E. I. Efimova, M. N. Varvanskaya, and L. G. Tereshchenko, *Khim. Geterotsikl. Soedin.*, 1644 (1972).

¹¹⁴³ J. Rebek, J. E. Trend, R. V. Wattle, and S. Chakravorti, *J. Am. Chem. Soc.* **101**, 4333 (1979).

¹¹⁴⁴ J. Rebek and R. V. Wattle, *J. Am. Chem. Soc.* **102**, 4853 (1980).

¹¹⁴⁵ E. Buhleier, W. Wehner, and F. Vogtle, *Chem. Ber.* **111**, 200 (1978).

chloride of the 4,4'-dicarboxylic acid reacts with alkyl cadmium reagents to afford the corresponding 4,4'-diketones.¹¹⁴⁰ Interestingly, dimethyl 2,2'-bipyridine-3,3'-dicarboxylate with excess methyllithium affords the diol **102**, which cyclizes in the presence of hot sulfuric acid to **103**.¹¹⁴⁶



Bromo substituents in the 6- and 6'-positions of 2,2'-bipyridines are particularly reactive, being readily converted to amino,⁴⁰⁸ cyano,^{408,819} alkoxy,⁴²³ hydrazino,^{1147,1148} chloro,⁴²³ and hydrogen groups⁴²³ and by way of the corresponding lithio derivatives to carboxyl, methyl, aldehyde or alkylcarbonyl,⁵¹⁶ and other groupings.¹¹⁴⁹⁻¹¹⁵¹ 6,6'-Dibromo-2,2'-bipyridine also reacts with the disodium derivatives of polyethylene glycols to give crown ethers akin to **100**,¹¹⁵² and 6,6'-bis(chloromethyl)-2,2'-bipyridine^{1151,1153} and the derived 6,6'-bis(mercaptomethyl)-2,2'-bipyridine

¹¹⁴⁶ J. Rebek and J. E. Trend, *J. Am. Chem. Soc.* **100**, 4315 (1978).

¹¹⁴⁷ J. Lewis and K. P. Wainwright, *J. C. S. Chem. Commun.*, 169 (1974).

¹¹⁴⁸ J. Lewis and K. P. Wainwright, *J. Chem. Soc. Dalton*, 440 (1978).

¹¹⁴⁹ G. R. Newkome and D. C. Hager, *J. Org. Chem.* **43**, 947 (1978).

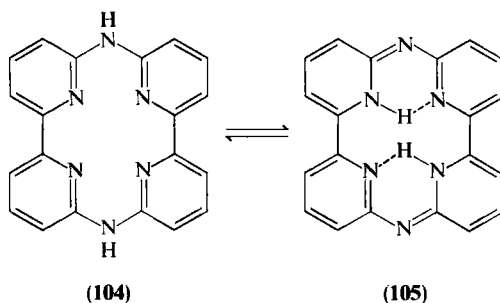
¹¹⁵⁰ G. R. Newkome, M. Onishi, W. E. Puckett, and W. A. Deutsch, *J. Am. Chem. Soc.* **102**, 4551 (1980).

¹¹⁵¹ G. R. Newkome, D. K. Kohli, and F. Fronczek, *J. C. S. Chem. Commun.*, 9 (1980).

¹¹⁵² G. R. Newkome, A. Nayak, F. Fronczek, T. Kawato, H. C. R. Taylor, L. Meade, and W. Mattice, *J. Am. Chem. Soc.* **101**, 4472 (1979).

¹¹⁵³ G. R. Newkome, D. K. Kohli, F. R. Fronczek, B. J. Hales, E. E. Case, and G. Chiari, *J. Am. Chem. Soc.* **102**, 7608 (1980).

participate in similar reactions.¹¹⁵⁴ Bromo substituents in the 4- and 4'-positions have also been replaced by nucleophiles.³²⁷ 5-Bromo-2,2'-bipyridine reacts under more vigorous conditions, for example, with aqueous alkali under pressure to afford 5-hydroxy-2,2'-bipyridine.⁷⁷⁹ Although chloro groups are not as reactive as bromo⁸¹⁹ the chloro groups in the 4,4',6,6' positions of octachloro-2,2'-bipyridine are replaced readily by fluorine, whereas the 4,4'-fluoro groups in octafluoro-2,2'-bipyridine are similarly replaced by methoxyl. Under drastic conditions all the chlorine atoms in octachloro-2,2'-bipyridine are replaced by fluorine.⁷⁷⁷ Likewise the halogen atom in 4-chloro-2,2'-bipyridine has been replaced by amines and thiophenol.³²⁶ In an interesting reaction, 6,6'-dichloro-2,2'-bipyridine was converted to the macrocycle **104** by a template cyclization involving a zinc complex followed by demetallation. Some 6,6'-diamino-2,2'-bipyridine was formed as a by-product. The macrocycle **104** is in tautomeric equilibrium with the imine form **105**, which is preferred in non-polar solvents. Some reactions of **104** were investigated.⁸⁹⁷



Cyano substituents are readily hydrolyzed to the corresponding carboxylic acid^{408,780,782} and converted to carbothioamides⁹⁰⁵ and hydrazidine, triazine,^{819,1155,1156} and triazoline substituents by appropriate reagents,^{1155,1156} whereas hydrazine-substituted 2,2'-bipyridines afford ready access to the corresponding pyrazolyl substituted analogs.¹¹⁴⁸ Reduction of the cyano group of 4-methoxy-6-cyano-2,2'-bipyridine by lithium aluminum hydride, followed by reaction with acid and hydroxylamine hydrochloride, affords a synthesis of the natural product caerulomycin (**7**).⁷ Sulfonic acid groups in the 5- and 5'-positions of 2,2'-bipyridine have been replaced by hydroxyl or cyano groups by the usual fusion procedures^{780,782} and converted to sulfonamides.⁷⁸² On heating the sodium salt of 2,2'-bipyridine-5-

¹¹⁵⁴ G. R. Newkome and D. K. Kohli, *Heterocycles* **15**, 739 (1981).

¹¹⁵⁵ F. H. Case, *J. Heterocycl. Chem.* **8**, 173 (1971).

¹¹⁵⁶ F. H. Case, *J. Heterocycl. Chem.* **10**, 353 (1973).

sulfonic acid to 500°C, 6,6'-bis(2-pyridyl)-3,3'-thiodipyridine is obtained.¹¹⁵⁷ 5-Hydroxy-2,2'-bipyridines have been converted to 5-alkoxy derivatives, using alkyl halides,⁷⁸² whereas the reverse procedure of dealkylation of alkoxy-2,2'-bipyridines to the hydroxyl derivatives is accomplished by the usual acid reagents.^{423,928} 3,5,3',5'-Tetrahydroxy-2,2'-bipyridine is reduced to 2,2'-bipyridine by zinc dust.⁴²³ 4-Hydroxy- (and 6-hydroxy)-2,2'-bipyridines normally exist, as expected in the pyridone tautomeric form, but some 4-hydroxy-3,5-dicarboxylic acid derivatives of 2,2'-bipyridine prefer the 4-hydroxy tautomeric form because of the presence of hydrogen bonding between the hydroxyl and the adjacent carbonyl groups.¹¹⁵⁸ Esters of 6-hydroxy-2,2'-bipyridines with carboxylic acids have been advocated as useful reagents for the selective acylation of alcohols⁹³² and the acylation of amines.⁵⁴⁷ 4-Amino-2,2'-bipyridines, however, usually prefer the amino tautomeric form, although the 4-tosylamido derivative probably exists as the imino tautomer in polar solvents.³²⁶

Diazotization of 4,4'-diamino-2,2'-bipyridine, followed by heating, affords 4,4'-dihydroxy-2,2'-bipyridine,⁹³¹ whereas a Sandmeyer reaction, using cuprous bromide, on diazotized 5,5'-diamino-2,2'-bipyridine gives 5,5'-dibromo-2,2'-bipyridine.¹¹³⁶ Heat resistant polymers are formed by condensation of 4,4'-diamino-2,2'-bipyridine with aromatic dianhydrides, such as pyromellitic anhydride,¹¹⁵⁹ whereas nitration of 4,4'-diamino-2,2'-bipyridine affords 5,5'-dinitro-4,4'-diamino-2,2'-bipyridine by rearrangement of the intermediate 4,4'-bis(nitroamino) compound. The nitro groups were subsequently reduced by hydrogen and palladium carbon to give 4,5,4',5'-tetraamino-2,2'-bipyridine.¹¹⁶⁰ Further nitration studies of amino-2,2'-bipyridines have been reported.^{421,1136} 3,3'-Dinitro-2,2'-bipyridine is reduced by stannous chloride and hydrochloric acid to 3,3'-diamino-2,2'-bipyridine, by palladized carbon and hydrogen to 3,3'-bis(hydroxyamino)-2,2'-bipyridine,⁴²¹ and by sodium sulfide to the tetraazaphenanthrene **106** (X = N=N),^{663,1161} and related reductions have been described.⁴¹⁸ Compound **106** (X = N=N) is also obtained from 3,3'-bis(hydroxyamino)-2,2'-bipyridine by dehydration with polyphosphoric acid.⁴²¹ Several standard transformations were performed on the amino groups of 3,3'-diamino-2,2'-bipyridine, the most interesting of which afforded structure **106** (X = NH) on reaction with zinc chloride and structure **106** (X = NHCSNH) with carbon disulfide.⁴²¹

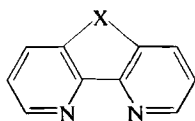
¹¹⁵⁷ P. M. Pojer and L. A. Summers, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **30B**, 980 (1975).

¹¹⁵⁸ R. Haller, *Tetrahedron Lett.*, 3175 (1965).

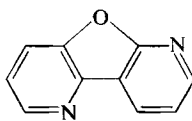
¹¹⁵⁹ K. Kurita and R. L. Williams, *J. Polym. Sci., Polym. Chem. Ed.* **11**, 3125 (1973).

¹¹⁶⁰ M. Balme and M. Gruffaz, French Patent 1,477,734 (1967) [*CA* **68**, 68889 (1968)].

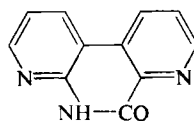
¹¹⁶¹ A. Etienne and G. Izoret, French Patent 1,369,401 (1964) [*CA* **62**, 570 (1965)].



(106)



(107)



(108)

2. 2,3'-Bipyridine

Several reactions of 2,3'-bipyridine carboxylic acids have been described. They are decarboxylated,^{96,552,564,588} esterified,^{554,589,1162} converted to amides,¹¹⁶² and hence to amines by the Hofmann degradation.¹¹⁶² The sterically hindered 2,3'-bipyridine-2,3'-dicarboxylic acid has been resolved,¹¹⁶² and the chromatographic behavior of some 2,3'-bipyridine carboxylic acids has been investigated.¹¹⁶³ The bromo substituent of 5-bromo-2,3'-bipyridine is replaced by hydroxyl under vigorous reaction conditions,⁵⁶⁷ by amino with ammonia,⁵⁶⁸ and by cyano with potassium ferricyanide.⁵⁶⁸ 5'-Bromo-2,3'-bipyridine likewise affords 5'-cyano-2,3'-bipyridine. 5-Bromo-2,3'-bipyridine participates normally in Grignard reactions, affording 5-ethyl-2,3'-bipyridine with magnesium and ethyl bromide. The resulting 5-ethyl-2,3'-bipyridine was oxidized by permanganate to 2,3'-bipyridine-5-carboxylic acid.¹¹⁶⁴ The 6-chloro substituent of 6-chloro-2,3'-bipyridine is readily replaced by amines.¹¹⁶⁵ Both 6-chloro- and 6'-chloro-2,3'-bipyridines are reductively dehalogenated by Raney nickel and hydrogen,^{18,584} although sometimes pyridine rings are reduced as well.⁵⁷¹ Condensation of 6-chloro-5-carbomethoxy-2,3'-bipyridine or the corresponding 5-cyano analog with hydrazine hydrate gives fused pyrazole derivatives,¹¹⁶⁶ and similar condensations afford other systems fused to the 2,3'-bipyridine nucleus.¹¹⁶⁵ The sulfonic acid group of 2,3'-bipyridine-5-sulfonic acid has been converted to the sulfonyl chloride and hence to sulfonamides¹¹⁶⁷ and replaced by hydroxyl or cyano by fusion with potassium hydroxide and potassium cyanide, respectively.⁵⁶⁴ Cyano substituents have been hydrolyzed,^{564,588,589,790} and 6- and 6'-hydroxyl substituents have been replaced by chloro with phosphorus oxychloride.^{18,571,584,589}

¹¹⁶² W. Brydowna, *Rocz. Chem.* **14**, 304 (1934).

¹¹⁶³ F. Kuffner and N. Faderl, *Monatsh. Chem.* **86**, 995 (1955).

¹¹⁶⁴ M. Goshav, O. S. Otroschenko, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.* **7**, 1213 (1971).

¹¹⁶⁵ P. Nantka-Namirski and L. Kaczmarek, *Acta Pol. Pharm.* **35**, 509 (1978).

¹¹⁶⁶ R. Balicki, L. Kaczmarek, and P. Nantka-Namirski, *Acta Pol. Pharm.* **33**, 289 (1976).

¹¹⁶⁷ T. K. Yusunov, K. Akbarov, and O. S. Otroschenko, *Uzb. Khim. Zh.*, **44** (1980) [*CA* **93**, 46370 (1980)].

4-Nitro-2,3'-bipyridine is reduced to 4-amino-2,3'-bipyridine by iron and acetic acid,⁹⁴³ and other similar reductions of nitro groups have been reported.⁵⁸⁸ 2',3-Diamino-2,3'-bipyridine on diazotization and heating affords **107**.¹¹⁶²

3. 2,4'-Bipyridine

Methyl-substituted 2,4'-bipyridines are oxidized by permanganate to the corresponding carboxylic acids,⁸⁹ which are readily decarboxylated.⁸⁹ Cyano groups in 2,4'-bipyridines have been hydrolyzed to the carboxylic acid.^{610,1168} 6-Hydroxy-2,4'-bipyridine affords 6-chloro-2,4'-bipyridine on reaction with phosphorus oxychloride.⁶¹⁰ The chloro group in this compound has been replaced by hydrazino, which on hydrogenation with Raney nickel led to 6-amino-2,4'-bipyridine. This latter compound on condensation with diethyl ethoxymethylenemalonate and subsequent ring closure afforded a pyridynaphthyridone derivative.⁶¹⁰ Condensation of 6-chloro-5-carbomethoxy-2,4'-bipyridine with hydrazine hydrate gives a fused pyrazole compound.¹¹⁶⁶ A difluoro-2,4'-bipyridine has been converted to an ethoxy derivative,⁵⁹⁴ whereas 3'-methoxy-2',6'-diphenyl-2,4'-bipyridine on ether cleavage afforded 3'-hydroxy-2',6'-diphenyl-2,4'-bipyridine, which reacted with an oxidizing agent, such as ferricyanide or PbO₂, to produce a paramagnetic species.⁶⁰⁷ 3,3'-Dinitro-2,4'-bipyridine on reduction by sodium sulfide afforded 2,5,9,10-tetraazaphenanthrene, which lost nitrogen on pyrolysis to give the corresponding diazabiphenylene.⁴²² 2,4'-Bipyridine analogs of amoxicillin have been prepared.¹¹⁶⁹

4. 3,3'-Bipyridine

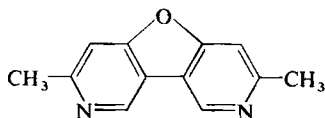
4-Methyl-3,3'-bipyridine has been oxidized by permanganate to 3,3'-bipyridine-4-carboxylic acid.⁵⁷⁴ 3,3'-Bipyridine carboxylic acids are easily decarboxylated^{96,97,588,631} and have been esterified^{613,1170} and converted to amides,^{615,1170} hydrazides,^{613,615} and acylazides.⁶¹³ The Hofmann degradation, of the diamide of 3,3'-bipyridine-2,2'-dicarboxylic acid affords the expected 2,2'-diamino-3,3'-bipyridine, but some of the tricyclic system **108** is formed as well.¹¹⁷⁰ A 2,2'-bis(acylazide) is converted to a similar tricyclic system with ethanol via the intermediate isocyanate, and several related reactions have been described.⁶¹³ The simultaneous dehydration

¹¹⁶⁸ R. P. Brundage and G. Y. Leshner, U.S. Patent 3,928,366 (1975) [CA **84**, 74253 (1976)].

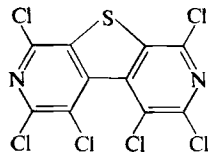
¹¹⁶⁹ T. F. Mich, U.S. Patent 4,092,309 (1978) [CA **89**, 163569 (1978)].

¹¹⁷⁰ W. Brydowna and W. Wiszniewski, *Rocz. Chem.* **15**, 378 (1935).

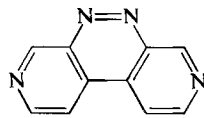
and decarboxylation of 6,6'-dimethyl-4,4'-dihydroxy-3,3'-bipyridine-2,2'-dicarboxylic acid afford compound **109** by heating at 140°C.⁶¹⁵ The sterically hindered 2,4,2',4'-tetracarboxy-6,6'-diphenyl-3,3'-bipyridine has been resolved.⁶¹⁴ 5-Bromo-3,3'-bipyridine is converted to the 5-hydroxy analog with aqueous alkali under pressure,⁷⁷⁹ whereas the fluoro groups at positions 4,4',6,6' in octafluoro-3,3'-bipyridine are the most reactive to such nucleophiles as alkoxide and amines. Methylolithium reacts with this compound to afford 6-methylheptafluoro-3,3'-bipyridine. The ¹⁹F NMR spectra of several of these polyfluoro compounds were included in the study.⁶²³ 3,3'-Bipyridine-5-sulfonic acid is converted to the 5-cyano^{773,793} or 5-hydroxy⁷⁷³ derivatives of 3,3'-bipyridine by reaction with potassium ferricyanide or potassium hydroxide, respectively. Cyano substituents have been hydrolyzed to the corresponding carboxylic acid,^{588,631,773,793} and the hydroxy groups in 4,4'-dihydroxy-3,3'-bipyridine were converted to chloro groups with phosphorus halides and hence to hydrogen by reductive dehalogenation via the 4,4'-diiodo analog.⁶⁴⁰ Acyl derivatives of 6,6'-diamino-3,3'-bipyridine have been prepared,⁶²¹ and 6-aminoheptafluoro-3,3'-bipyridine was oxidized by peroxytrifluoroacetic acid to the 6-nitro derivative.⁶²³ Nitro substituents have been reduced to amino groups.⁵⁸⁸ 2,2'-Diamino- and 4,4'-diamino-3,3'-bipyridines cyclize internally with loss of ammonia, using zinc chloride, to afford the corresponding diazacarbazole.⁹⁵⁵ Reactions applied to the hydroxy-3,3'-bipyridinone **59** related to indigoidine (**20**) include oxidation, reduction, methylation, acetylation, and amination by standard procedures.^{80,81,83,636}



(109)



(110)



(111)

5. 3,4'-Bipyridine

Methyl substituents in 3,4'-bipyridines have been oxidized by permanganate to the corresponding carboxylic acids,⁸⁹ which are readily decarboxylated,^{89,211,588,641} and esters have been converted to amides.⁵⁹⁸ 3,4'-Bipyridine-3'-sulfonic acid on fusion with potassium ferricyanide affords 3'-cyano-3,4'-bipyridine.⁷⁹⁵ Cyano-substituted 3,4'-bipyridines have been hydrolyzed to the amide or carboxylic acid,^{588,653,654} and the amides were converted to amino groups.⁶⁵⁷ Hydroxyl substituents in the 2',6',6'-positions of 3,4'-bipyridine have been replaced by chloro groups with phosphorus

halides,^{644,650,654} whereas 3'-methoxy-2',6'-diphenyl-3,4'-bipyridine on ether cleavage affords the 3'-hydroxy analog, which is oxidized by ferricyanide or PbO₂ to a free radical.⁶⁰⁷ The bromo substituent of 5-bromo-3,4'-bipyridine-6-one is replaced by hydroxyl under vigorous conditions,⁷⁹⁶ whereas 5-cyano-6-chloro-3,4'-bipyridine condenses with hydrazine to afford a fused pyrazole derivative,¹¹⁷¹ and 5-carbomethoxy analogs behave likewise.^{1172,1173} Diazotization of certain amino-3,4'-bipyridines, followed by heating, gives the expected hydroxy analog,⁶⁴⁴ whereas 5,6-diamino-3,4'-bipyridine gives an imidazole derivative on condensation with triethoxymethane.¹¹⁷⁴ Nitro substituents have been reduced to amino.^{588,653}

6. 4,4'-Bipyridine

Standard substituent transformations have likewise been reported in 4,4'-bipyridines. Methyl to carboxyl,^{712-714,1175,1176} decarboxylation of carboxyl,^{91,712-716,775,1175} cyano to carboxyl,⁷⁷⁵ esters to amides,⁵⁹⁸ 2-hydroxyl to 2-chloro,^{644,650-652} sulfonic acid groups to cyano^{775,799} or hydroxyl,⁷⁷⁵ diazotized amino groups to hydroxyl⁶⁴⁴ or bromo,⁶⁶³ and nitro to amino^{663,955} have all been described. 3,3'-Bis(2-piperidyl)-4,4'-bipyridines are oxidized to 4,4'-bipyridine-3,3'-dicarboxylic acid by permanganate,^{715,716} whereas 3-methoxy-2,6-diphenyl-4,4'-bipyridine on ether cleavage affords the 3-hydroxy analog, which on treatment with ferricyanide gives a free radical.⁶⁰⁷ 2,2'-Dimethyl-4,4'-bipyridine, on treatment with butyllithium, followed by 1-chloro-3-iodopropane, gives 2,2'-bis(4-chlorobutyl)-4,4'-bipyridine, which intramolecularly quaternizes the pyridine nitrogens to produce a biquinolizinium diquaternary system.⁹⁶⁸ There has been much interest in polychloro-4,4'-bipyridines. Octachloro-4,4'-bipyridine reacts with butyllithium to afford the 3-lithioheptachloro or 3,3'-dilithiohexachloro analogs. The former reacts with water to give heptachloro-4,4'-bipyridine, with dimethyl sulfate to give 3-methylheptachloro-4,4'-bipyridine, and with ethylene oxide to afford the 3- β -hydroxyethyl derivative and the related fused furan ring-closed product.^{1177,1178} Several similar replacements of the lithio group were also reported.¹¹⁷⁷ Octachloro-4,4'-bipyridine on reaction

¹¹⁷¹ G. Y. Leshner and M. D. Gruett, U.S. Patent 4,264,603 (1981) [CA 95, 62198 (1981)].

¹¹⁷² G. Y. Leshner and M. D. Gruett, U.S. Patent 4,264,612 (1981) [CA 95, 62011 (1981)].

¹¹⁷³ G. Y. Leshner and M. D. Gruett, U.S. Patent 4,265,895 (1981) [CA 95, 62200 (1981)].

¹¹⁷⁴ G. Y. Leshner, C. J. Opalka, and D. F. Page, U.S. Patent 4,276,293 (1981) [CA 95, 203948 (1981)].

¹¹⁷⁵ A. Heuser and C. Stoeck, *J. Prakt. Chem.* **44**, 404 (1891).

¹¹⁷⁶ F. Huth, *Ber. Dtsch. Chem. Ges.* **32**, 2209 (1899).

¹¹⁷⁷ J. D. Cook, N. J. Foulger, and B. J. Wakefield, *J. C. S. Perkin I*, 995 (1972).

¹¹⁷⁸ N. J. Foulger and B. J. Wakefield, *J. C. S. Perkin I*, 871 (1974).

with butyllithium and then iodine similarly gives heptachloro-3-iodo- and hexachloro-3,3'-diiodo-4,4'-bipyridines.¹¹⁷⁹ 3,3'-Dilithio-hexachloro-4,4'-bipyridine with water affords likewise the hexachloro-4,4'-bipyridine, and other similar reactions were reported. Interestingly, with sulfur dichloride it afforded the hexachlorothienodipyridine **110**.⁶⁷³ This compound and related polychloro-4,4'-bipyridines have subsequently been the subject of quantum chemical calculations in conjunction with ³⁵Cl-NQR determinations.¹¹⁸⁰ In octachloro-4,4'-bipyridine, as expected, the 2,2'-positions are the most reactive to nucleophilic attack. Reaction with piperidine affords the 2,2'-bispiperidino analog,¹¹⁷⁷ and similar replacements with amines and hydrazine and subsequent transformations have been described.¹¹⁸¹ 3-Fluoro- and 3,3'-difluoro-4,4'-bipyridines have also been converted to the corresponding ethoxy and hydrazino derivatives.⁵⁹⁴ Photolysis of octachloro-4,4'-bipyridine results in loss of some halogens when the reaction is conducted in ethanol but irradiation in carbon tetrachloride gave no reaction. Likewise, photolysis of hexachloro-3,3'-diiodo-4,4'-bipyridine in ether afforded the hexachloro-4,4'-bipyridine, but photolysis in carbon tetrachloride resulted in replacement of iodine by chlorine to give octachloro-4,4'-bipyridine.¹¹⁷⁹ 3,3'-Dinitro-4,4'-bipyridine on reduction by sodium sulfide affords the tetraazaphenanthrene **111**, which was pyrolyzed with loss of nitrogen to the diazabiphenylene.^{663,1182} Reduction by arsenious oxide afforded a bis-*N*-oxide of **111**. 3,3'-Diamino-4,4'-bipyridine cyclizes internally with loss of ammonia, using zinc chloride to afford the corresponding diaza-carbazole.⁹⁵⁵

G. MISCELLANEOUS REACTIONS

2,2'-Bipyridine and 4,4'-bipyridine form molecular complexes with halogenated nitrophenols.^{1183,1184} The former also complexes with urea, thiourea and related compounds,¹¹⁸⁵ benzyl alcohol, phenol,¹¹⁸⁶ acetic

¹¹⁷⁹ J. Bratt, B. Iddon, A. G. Mack, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, *J. C. S. Perkin I*, 648 (1980).

¹¹⁸⁰ M. Redshaw, *Org. Magn. Reson.* **7**, 358 (1975).

¹¹⁸¹ B. J. Wakefield, *J. Organometal. Chem.* **99**, 191 (1975).

¹¹⁸² J. A. H. MacBride, *J. C. S. Chem. Commun.*, 359 (1974).

¹¹⁸³ B. V. Tronov and O. A. Terekhova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **3**, 466 (1960) [*CA* **54**, 24729 (1960)].

¹¹⁸⁴ N. V. Zubtsova, G. L. Ryzhova, and O. A. Terekhova, *Tr. Tomsk. Gos. Univ.* **192**, 194 (1968) [*CA* **74**, 124358 (1971)].

¹¹⁸⁵ G. Oepen and F. Vogtle, *Justus Liebigs Ann. Chem.*, 2114 (1979).

¹¹⁸⁶ K. Kimura and R. Fujishiro, *Bull. Chem. Soc. Jpn.* **34**, 304 (1961).

anhydride,¹¹⁸⁷ trifluoroacetic acid,¹¹⁸⁸ fluorosulfonic acid (FSO₃H),¹¹⁸⁹ hexachlorocyclohexane,¹¹⁹⁰ iodine cyanide, and iodoacetylenes,¹¹⁹¹ whereas the latter forms complexes with 1,3,5-trinitrobenzene,¹¹⁹² cyclodextrins,¹¹⁹³ and various phenols.¹¹⁹⁴ There has been considerable interest in complexes of these two bipyridines with 7,7,8,8-tetracyanoquinodimethane and its radical anion,^{1084,1195-1199} including studies of their electrical resistivity, magnetic susceptibilities,^{1200,1201} suitability as electrodes,¹²⁰² and ESR spectra.¹²⁰³ Exciplex complexes of 2,2'- and 4,4'-bipyridines with *N,N*-diethylaniline have been prepared, and their fluorescence has been studied.¹²⁰⁴ Exchange of hydrogen for deuterium has been noted to occur in the 6 position in the alkali-metal complexes of 2,2'-bipyridine.^{1205,1206} Tritium-labeled 2,2':6',2''-terpyridine has been prepared.¹²⁰⁷

Sulfur bridging of 2,2'-, 3,3'-, and 4,4'-bipyridines by reaction with hydrogen sulfide over alumina at 630°C affords a synthesis of thienodipyridines.^{1208,1209} For example, 2,2'-bipyridine gives compound 112. Somewhat similarly, dibromo-*N*-methylmaleimide with 4,4'-bipyridine forms

¹¹⁸⁷ K. C. Malhotra and D. S. Katoch, *Aust. J. Chem.* **27**, 1413 (1974).

¹¹⁸⁸ Z. Dega-Szafran, *Rocz. Chem.* **50**, 423 (1976).

¹¹⁸⁹ C. Belin, S. A. R. Pichvay, and J. Potier, *C. R. Hebd. Seances Acad. Sci., Ser. C* **291**, 53 (1980).

¹¹⁹⁰ S. Mager, M. Horn, I. Hopartean, and A. Motiu, *Monatsh. Chem.* **109**, 1403 (1978).

¹¹⁹¹ C. Laurence, M. Queignec-Cabanetos, T. Dziembowska, R. Queignec, and B. Wojtkowiak, *J. Am. Chem. Soc.* **103**, 2567 (1981).

¹¹⁹² J. J. Sudborough and S. H. Beard, *J. Chem. Soc.* **97**, 773 (1910).

¹¹⁹³ A. Ueno, H. Yoshimura, R. Saka, and T. Osa, *J. Am. Chem. Soc.* **101**, 2779 (1979).

¹¹⁹⁴ B. V. Tronov and O. A. Terekhova, *Tr. Tomsk. Gos. Univ., Ser. Khim.* **154**, 201 (1962) [*CA* **60**, 6820 (1964)].

¹¹⁹⁵ L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Am. Chem. Soc.* **84**, 3374 (1962).

¹¹⁹⁶ G. J. Ashwell, D. D. Eley, and M. R. Willis, *J. C. S. Faraday II*, **71**, 1227 (1975).

¹¹⁹⁷ G. Mihaly, K. Ritvay-Emandity, A. Janossy, K. Holczer, and G. Gruner, *Solid State Commun.* **21**, 721 (1977).

¹¹⁹⁸ K. Kamaras, G. Gruner, and G. A. Sawatzky, *Solid State Commun.* **27**, 1171 (1978).

¹¹⁹⁹ T. Kondo, K. Siratori, and H. Inokuchi, *J. Phys. Soc. Jpn.* **23**, 98 (1967).

¹²⁰⁰ K. Siratori and T. Kondo, *J. Phys. Soc. Jpn.* **27**, 301 (1969).

¹²⁰¹ M. Miljak, B. Korin, J. R. Cooper, K. Holczer, and A. Janossy, *J. Phys. (Orsay, Fr.)* **41**, 639 (1980).

¹²⁰² C. D. Jaeger and A. J. Bard, *J. Am. Chem. Soc.* **102**, 5435 (1980).

¹²⁰³ V. V. Pen'kovskii, *Teor. Eksp. Khim.* **5**, 183 (1969).

¹²⁰⁴ P. J. Harman, P. R. Nott, and B. K. Selinger, *Aust. J. Chem.* **30**, 1875 (1977).

¹²⁰⁵ M. Ishizuka and A. Ozaki, *Nippon Kagaku Kaishi*, 415 (1974).

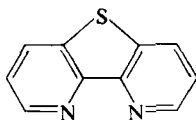
¹²⁰⁶ T. Nakamura, M. Soma, T. Onishi, and K. Tamaru, *Z. Phys. Chem. Wiesbaden [N. S.]* **89**, 122 (1974).

¹²⁰⁷ R. Hogg and R. C. Wilkins, *J. Chem. Soc.*, 341 (1962).

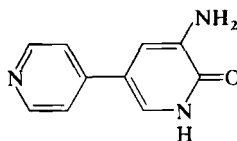
¹²⁰⁸ L. H. Klemm, D. R. McCoy, and C. E. Klopfenstein, *J. Heterocycl. Chem.* **8**, 383 (1971).

¹²⁰⁹ S. B. Mathur and L. H. Klemm, *Rev. Latinoam. Quim.* **5**, 150 (1974) [*CA* **82**, 43209 (1975)].

an anellated substitution product on irradiation.¹²¹⁰ Reaction of 3,3'-bipyridine by lithium diisopropylamide gave a low yield of a cyclotetrapyridine.¹²¹¹ Eutectic points are observed in the melting point diagrams of 2,2'-bipyridine with 2,2'-bithiazolyl¹²¹² or 4,4'-bithiazolyl,¹²¹³ whereas phase diagrams of the biphenyl 2,2'-bipyridine system have been investigated.¹²¹⁴



(112)



(113)

V. Uses

There are over 1500 references in the literature to uses of the bipyridines. In the space available it is impossible to deal comprehensively with them. We have, therefore, covered the major uses of the bipyridines by giving a few key references for each use.

One of the principal uses of 2,2'-bipyridine, 2,2':6',2''-terpyridine, and their derivatives is as analytical reagents for the determination of metals by virtue of their ability to complex with metals.^{1124,1215,1216} They have also been used analytically in biological systems because of their chelating properties. The biological effects of metal complexes of 2,2'-bipyridines have been reviewed.¹²¹⁷ 2,2'-Bipyridine and its derivatives have pronounced effects on many biological systems.¹²¹⁸⁻¹²²⁰ The activity in many, but not all, cases is due to the ability of 2,2'-bipyridine to complex with metals essential to the functioning of enzymes in living organisms. Furthermore, 2,2'-bipyridine stimulates the activity of some enzymes, perhaps by removing a metal that

¹²¹⁰ K. M. Wald, A. A. Nada, G. Szilagy, and H. Wamhoff, *Chem. Ber.* **113**, 2884 (1980).

¹²¹¹ T. Kauffmann, B. Greving, J. Konig, A. Mitschker, and A. Woltermann, *Angew. Chem., Int. Ed. Engl.* **14**, 713 (1975).

¹²¹² H. Erlenmeyer and E. H. Schmid, *Helv. Chim. Acta* **22**, 698 (1939).

¹²¹³ H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta* **22**, 938 (1939).

¹²¹⁴ S. A. Remyga, R. M. Myasnikova, and A. I. Kitaigorodskii, *Kristallografiya* **12**, 900 (1967).

¹²¹⁵ G. F. Smith, *Anal. Chem.* **26**, 1534 (1954).

¹²¹⁶ A. A. Schilt, "Analytical Applications of 1,10-Phenanthroline and Related Compounds." Pergamon, Oxford, 1969.

¹²¹⁷ A. Shulman and F. P. Dwyer, in "Chelating Agents and Metal Chelates" (F. P. Dwyer and D. P. Mellor, eds.), pp. 383-439. Academic Press, New York, 1964.

¹²¹⁸ H. P. Ehrlich and P. Bornstein, *Nature (London), New Biol.* **238**, 257 (1972).

¹²¹⁹ M. B. Lowe and J. N. Phillips, *Nature (London)* **194**, 1058 (1962).

¹²²⁰ K. V. Thimann and S. Satler, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 2770 (1979).

is inhibitory to the enzyme.¹²²¹ Some derivatives of 2,2'-bipyridine also have important activity in biological systems. In addition to the antibiotic caeculomycin (7) the most important biologically active derivative of 2,2'-bipyridine is the diquaternary salt **75** known as diquat dibromide, which is a valuable herbicide. It has been the subject of a monograph.⁴⁶⁷ In addition to their use as herbicides, diquaternary salts of 2,2'-bipyridine are useful as redox indicators and as one-electron transfer agents in biological systems.⁴⁶⁷ 2,2'-Bipyridine has also many uses in nonbiological areas. It acts as an activator of the polymerization of various olefins¹²²² and as a catalyst for a variety of chemical reactions.¹²²³ It improves the product in various metal-plating processes¹²²⁴ and is an ingredient of various copying materials.¹²²⁵ Several derivatives of 2,2'-bipyridines have also been found to be of value in nonbiological areas. Uses of diquat dibromide (**75**) and related diquaternary salts of 2,2'-bipyridine are often associated with their redox and one-electron transfer properties.⁴⁶⁷ They find use in various photographic developing processes.¹²²⁶ Diquat dibromide has been patented as an electrochemical voltage indicator¹²²⁷ and is useful in electrochromic display devices¹²²⁸ and as a quencher of the excited state of ruthenium complexes in light-energy conversion systems.⁸⁴⁵

2,3'-Bipyridine resembles nicotine in its pharmacological properties but is not as active.²⁰ The 3,4'-bipyridine derivative **113** known as amrinone and its relatives are of interest as cardiotonic agents.^{653,658,957,1229} 4,4'-Bipyridine has been tested as an insecticide, but it is not of practical value.¹²³⁰ It is used in the study of the electrochemistry of cytochrome *c*¹²³¹ and acts as a polymerization catalyst or hardening agent for various resins.¹²³² 1-Hexyl-4,4'-bipyridinium salts are especially effective as electron carriers in photochemical hydrogen producing systems.¹²³³ 1,1'-Dimethyl-4,4'-bipyridinium (**92**: R = R' = CH₃) and 1,1'-dibenzyl-4,4'-bipyridinium

¹²²¹ J. W. Earl and I. R. Kennedy, *Phytochemistry* **14**, 1507 (1975).

¹²²² S. Miertus, O. Kysel, and P. Majek, *Chem. Zvesti* **33**, 153 (1979).

¹²²³ L. G. Cannell, *J. Am. Chem. Soc.* **94**, 6867 (1972).

¹²²⁴ K. E. Langford, *Electroplat. Met. Finish.* **9**, 39 (1956).

¹²²⁵ H. Ishii, T. Tanaka, and A. Yamada, Japanese Patent 101,111 (1977) [*CA* **88**, 172078 (1978)].

¹²²⁶ J. F. Willems, *J. Photogr. Sci.* **19**, 113 (1971).

¹²²⁷ B. I. Shapiro and V. V. Treier, U.S.S.R. Patent 324,583 (1971) [*CA* **77**, 13304 (1972)].

¹²²⁸ K. Imamura, M. Takada, I. Nagata, and Y. Hara, Japanese Patent 37,078 (1979) [*CA* **91**, 99962 (1979)].

¹²²⁹ A. A. Alousi, A. E. Farah, G. Y. Leshner, and C. J. Opalka, *Circ. Res.* **45**, 666 (1979).

¹²³⁰ C. R. Smith, C. H. Richardson, and H. H. Shephard, *J. Econ. Entomol.* **23**, 863 (1930).

¹²³¹ W. J. Albury, M. J. Eddowes, H. A. O. Hill, and A. R. Hillman, *J. Am. Chem. Soc.* **103**, 3904 (1981).

¹²³² Y. Imanishi, S. Nagoaka, and T. Higashimura, *Polym. J.* **4**, 644 (1973).

¹²³³ I. Tabushi and A. Yazaki, *Tetrahedron* **37**, 4185 (1981).

(92: $R = R' = C_6H_5CH_2$) diquatery salts have been used extensively in biological systems as one-electron transfer agents and as redox indicators under the names *methyl viologen* and *benzyl viologen*, respectively.⁴⁶⁷ The salt **92** ($R = R' = CH_3$) is also the important herbicide paraquat, which is the subject of a monograph.⁴⁶⁷ It also promotes oleoresin formation in pine trees. 1,1'-Dialkyl diquatery salts of 4,4'-bipyridine have also been utilized extensively in nonbiological areas. Most of these uses likewise depend on the one-electron redox properties of the salts and on the deep color of their radical cations.^{389,467,1226} Of particular interest is the use of 1,1'-dialkyl diquatery salts of 4,4'-bipyridine, especially the 1,1'-diheptyl compound, as the main components of electrochromic memory display devices¹²³⁴ and semiconductor electrodes.¹²³⁵ Another important recent use of paraquat and related diquatery salts of 4,4'-bipyridines is in renewable energy research. They act as electron-transfer agents in a variety of systems designed to accomplish photolysis of water to hydrogen and oxygen by utilizing, for example, solar energy and other irradiation.^{845,1236-1238} Other uses of diquatery salts of 4,4'-bipyridine include acting as electron acceptors in fast reaction techniques such as pulse radiolysis, especially from reactive biradicals.¹²³⁹ Viologen polymers act as redox polymers.¹²⁴⁰

¹²³⁴ R. C. Cieslinski and N. R. Armstrong, *J. Electrochem. Soc.* **127**, 2605 (1980).

¹²³⁵ N. S. Lewis and M. S. Wrighton, *Science* **211**, 944 (1981).

¹²³⁶ C. Laane, W. E. Ford, J. W. Otvos, and M. Calvin, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 2017 (1981).

¹²³⁷ J. R. Darwent, I. McCubbin, and G. Porter, *J. C. S. Faraday II* **78**, 903 (1982).

¹²³⁸ M. Graetzel, *Acc. Chem. Res.* **14**, 376 (1981).

¹²³⁹ J. C. Scaiano, M. V. Encinas, and M. V. George, *J. C. S. Perkin II*, 724 (1980).

¹²⁴⁰ A. Factor and T. O. Rouse, *J. Electrochem. Soc.* **127**, 1313 (1980).

The 2*H*-Imidazoles

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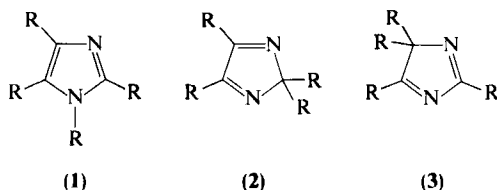
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2. N-Linked	410
3. O-Linked	412

I. Introduction

As is the case with the 1*H*-pyrroles¹ and the 1*H*-pyrazoles,² structures isomeric with the 1*H*-imidazoles (**1**) exist that are nonaromatic because of the presence of a tetrahedral carbon atom in the ring. These structures, the 2*H*-imidazoles (**2**) and 4*H*-imidazoles (**3**), have properties quite different from their 1*H* counterparts. They also differ from each other in that the polarities of the two conjugated C=N bonds reinforce one another in structures **3**, but are in opposition in structures **2**.



¹ M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **32**, 234 (1982).

² M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **34**, 1, 53 (1983).

Reviews on 1*H*-imidazoles (1),³⁻⁵ have mentioned only isolated examples of the iso compounds **2** and **3**, although a later treatise has covered the latter two classes in more detail.⁶ The present review seeks to cover all known 2*H*-imidazoles, whereas the following one⁷ will deal with the 4*H* compounds. *Chemical Abstracts* have been covered up to and including issue 4 of Volume 97, using a comprehensive CAS "on line" substructure search; a few additional references are included from the more common international journals. The search excluded structures with exocyclic double bonds, and hence those fused to a benzene ring.

II. Synthesis of 2*H*-Imidazoles

The most important synthetic routes have been from ketones by cyclization, by the transformation of imidazolone derivatives, and by the reaction between 1*H*-imidazoles and electrophiles.

A. FROM KETONES BY CYCLIZATION

1. α -Diketones and a Second Ketone

The reaction between an aldehyde and an α -diketone in the presence of an ammonia source is an important route to 1*H*-imidazoles.⁵ When the aldehyde is replaced by a second ketone, a 2*H*-imidazole is the product (Scheme 1).⁸⁻¹² Optimum yields are obtained by heating with 10 mol ammonium acetate as a 2.5 *M* solution in acetic acid¹⁰ and are in the range 20–80%.

³ K. Hofmann, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Part 1 p. 363. Wiley (Interscience), New York, 1953.

⁴ A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Russ Chem. Rev. (Engl. Transl.)* **35**, 122 (1966).

⁵ M. R. Grimmett, *Adv. Heterocycl. Chem.* **12**, 103 (1970); **27**, 241 (1980).

⁶ M. R. Grimmett, in "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky and C. W. Rees, eds.), Vol. 4, Chapters 4.6–4.8. Pergamon, Oxford, 1984.

⁷ M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **35**, 413 (1983).

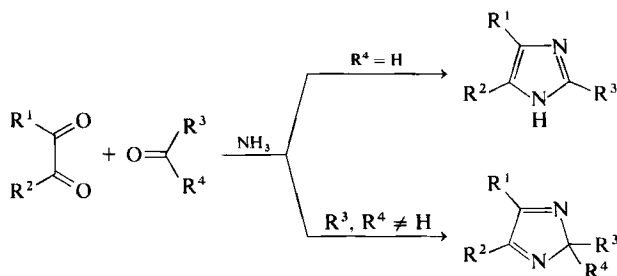
⁸ M. Weiss, *J. Am. Chem. Soc.* **74**, 5193 (1952).

⁹ F. Fariña, *An. R. Soc. Espan. Fis. Quim., Ser. B* **49**, 599 (1953) [*CA* **48**, 4524 (1954)].

¹⁰ J. H. M. Hill, T. R. Fogg, and H. Guttmann, *J. Org. Chem.* **40**, 2562 (1975).

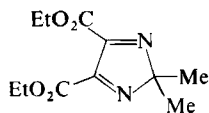
¹¹ A. R. Katritzky, S. Bravo-Borja, J. Marquet, and M. P. Sammes, *J. C. S. Perkin I*, 2065 (1983).

¹² A. G. Hortmann, J.-Y. Koo, and C.-C. Yu, *J. Org. Chem.* **43**, 2289 (1978).

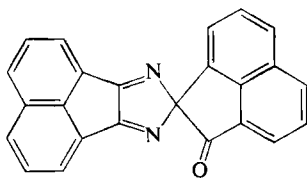


SCHEME 1

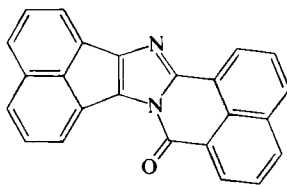
The diketone has normally been benzil, although diethyl 2,3-dioxobutane-1,4-dioate gives **4**,⁹ and phenylglyoxal gives the expected product,¹² both with propanone. A reaction involving 2,3-butanedione and 2-butanone led only to a very low yield of a 2*H*-imidazole.¹³ When the diketone serves also as the second carbonyl component, a rearranged product is isolated.^{8,14} Thus acenaphthenequinone yields **6**¹⁴ rather than **5**, as had been claimed earlier,¹⁵ via migration of the acyl group; phenanthraquinone, in contrast, is converted only to a diimine.¹⁴



(4)



(5)



(6)

Substituents R^3 and R^4 have been alkyl,^{8-10,12} ethoxycarbonyl,¹¹ benzyl,^{8,10} substituted benzyl,¹⁰ and phenyl^{8,10,12}; the latter gave the lowest yield. Cyclobutanone gave a rearranged product, due apparently to ring strain.¹⁰

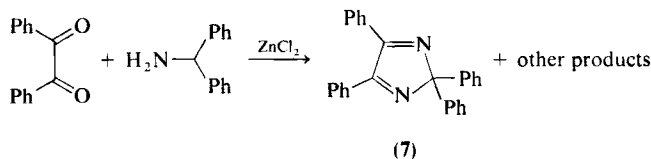
¹³ F. Asinger and W. Leuchtenberger, *Justus Liebigs Ann. Chem.*, 1183 (1974).

¹⁴ D. M. White, *J. Org. Chem.* **35**, 2452 (1970).

¹⁵ O. Tsuge and M. Tashiro, *Bull. Chem. Soc. Jpn.* **36**, 970 (1963); **39**, 2477 (1966).

2. Other Routes from α -Diketones

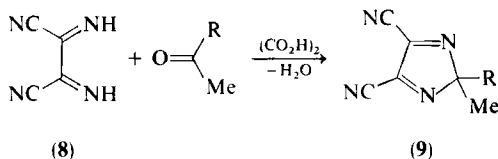
In the presence of zinc chloride, benzil and 1,1-diphenylmethanamine yield a small amount of 2,2,4,5-tetraphenyl-2H-imidazole (7, Scheme 2).¹⁶ A claim¹⁷ to have isolated a 2-benzoyl-2H-imidazole from benzil monohydrazone and S_4N_4 was later shown to be in error.¹⁸



SCHEME 2

3. α -Diimines and Ketones

The acid-catalyzed condensation between alkyl methyl ketones and the diiminodinitrile **8** (Scheme 3), with removal of water, yields the dinitriles **9**¹⁹⁻²²; the reaction fails with other ketones.²¹ 2,2-Dimethoxypropane in tetrahydrofuran (THF) gives a high yield of **9** ($R = Me$).²¹



SCHEME 3

4. Ketones, Ammonia, and Sulfur

Dialkyl ketones **10** (Scheme 4) react with ammonia and excess sulfur at low temperature to give moderate yields of 2H-imidazoles **11**.¹³ The method complements those above in allowing the introduction of alkyl substituents into the 4- and 5-positions of the ring. Methyl ketones (**10**: $R^2 = H$), in

¹⁶ K. N. Mehrotra and B. P. Giri, *Indian J. Chem., Sect. B* **18B**, 374 (1979).

¹⁷ M. Tashiro and S. Mataka, *Heterocycles* **4**, 1243 (1976).

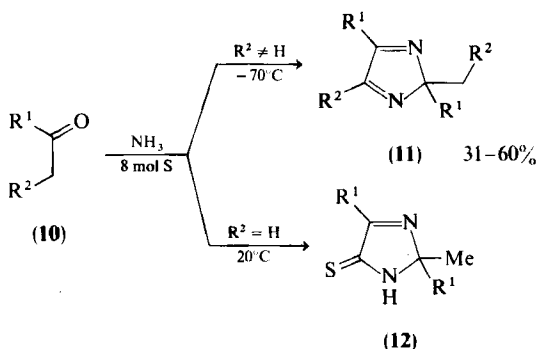
¹⁸ S. T. A. K. Daley and C. W. Rees, *Tetrahedron Lett.* **22**, 1759 (1981).

¹⁹ R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard, and O. W. Webster, *J. Am. Chem. Soc.* **93**, 4953 (1971).

²⁰ O. W. Webster, *Angew. Chem., Int. Ed. Engl.* **11**, 153 (1972).

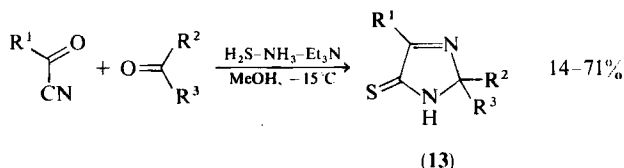
²¹ R. W. Begland and D. R. Hartter, *J. Org. Chem.* **37**, 4136 (1972).

²² D. R. Hartter, U.S. Patent 3,709,900 (1973) [*CA* **78**, 72138 (1973)]



SCHEME 4

contrast, are converted to the 2*H*-imidazolethiones **12**,^{23–26} and yields when $\text{R}^1 = \text{alkyl}$ are improved by addition of piperidine. A mechanism has been suggested involving an α -oxothionamide²⁴ and is supported by the isolation of 2*H*-imidazolinethiones **13** from acyl nitriles and a ketone with hydrogen sulfide (Scheme 5).²⁷ Since **12** and **13** are readily convertible to a variety of 2*H*-imidazoles (Section II,B), the reaction in Scheme 5 is important in giving products in which R^1 , R^2 , and R^3 may all be different. Improved methods for preparing acyl nitriles have been reported recently.²⁸



SCHEME 5

A reaction related to the preparation of **11** is the cyclization of α -bromo-ketones with ammonia and a second ketone to give imidazolines **14**, which are oxidized by sulfur in high yields to 2*H*-imidazoles **15** (Scheme 6).²⁹

²³ F. Asinger, W. Schäfer, G. Baumgarte, and P. F. Müting, *Justus Liebigs Ann. Chem.* **661**, 95 (1963).

²⁴ F. Asinger and H. Offermanns, *Angew. Chem., Int. Ed. Engl.* **6**, 907 (1967), and references cited therein.

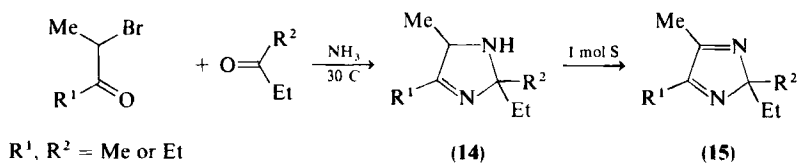
²⁵ F. Asinger, H. Offermanns, D. Neuray, and F. Abo Dagga, *Monatsh. Chem.* **101**, 500 (1970).

²⁶ W. Reid and E. Nyiondi-Bonguen, *Justus Liebigs Ann. Chem.*, 134 (1973).

²⁷ F. Asinger, W. Schäfer, and F. Haaf, *Justus Liebigs Ann. Chem.* **672**, 134 (1964); F. Asinger, A. Saus, H. Offermanns, and H.-D. Hahn, *ibid.* **691**, (1966).

²⁸ H. Klenk, H. Offermanns, and W. Schwarze, *Ger. Offen.* 2,708,183 (1978) [*CA* **89**, 179844 (1978)]; K. Haase and H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **21**, 83 (1982).

²⁹ F. Asinger, M. Thiel, and R. Sowada, *Monatsh. Chem.* **90**, 402 (1959).



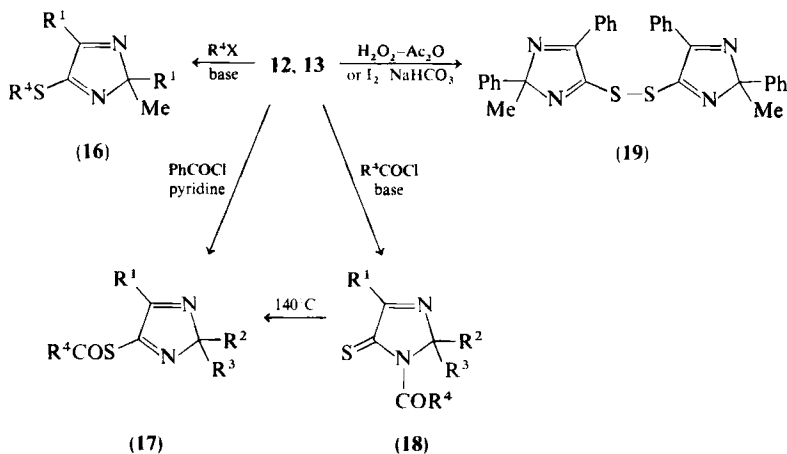
SCHEME 6

B. BY TRANSFORMATION OF 2*H*-IMIDAZOLE-5-THIONES

Conversion of the $\text{S}=\text{C}-\text{NH}$ moiety in the 2*H*-imidazoletiones **13** to $\text{X}-\text{C}=\text{N}$, where X is a single-bonded group, generates the 2*H*-imidazole ring system. This has been accomplished in a number of ways, generally in high yields.

1. Electrophilic Attack at Sulfur

Treatment of **13** with dimethyl sulfate,^{27,30,31} or other alkyl halides,^{27,32} and base leads to the thioalkyl derivatives **16** in high yields (Scheme 7). The oxo analog of **12** ($\text{R}^1 = \text{Ph}$) is methylated at the ring nitrogen atom.²⁷



SCHEME 7

³⁰ F. Asinger and W. Leuchtenberger, *Justus Liebigs Ann. Chem.*, 157 (1974).

³¹ A. Maquestiau, Y. Van Haverbeke, J. C. Vanovervelt, M. Lambert, and A. Ravach, *Bull. Soc. Chim. Belg.* **86**, 967 (1977).

³² F. Asinger, W. Schäfer, A. Wegerhoff, and G. Kriebel, *Monatsh. Chem.* **97**, 792 (1966).

Acylation of **13** with benzoyl chloride and pyridine gives **17** ($R^1 = R^2 = R^4 = \text{Ph}$, $R^3 = \text{Me}$) and a little of the *N*-benzoyl isomer **18**²⁷; the sodium salts of **13**, however, yield only **18**.³³

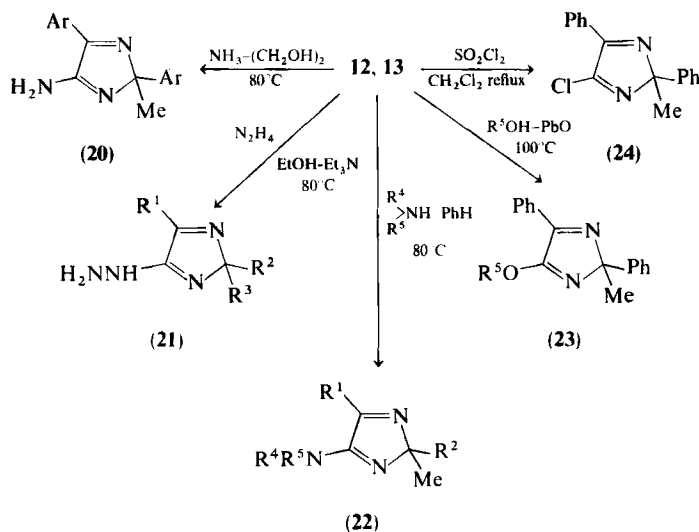
Mild oxidation converts **12** ($R^1 = \text{Ph}$) to the disulfide **19**.³²

2. Migration to Sulfur

On heating to 140°C in the absence of a solvent, the *N*-acyl compounds **18** rearrange quantitatively to the isomeric structures **17**.³⁴ The rate of reaction is increased by bulky ring substituents, being immeasurably slow when $R^1 = R^2 = R^3 = \text{Me}$; it also depends on the nature of R^4 . Crossing experiments have shown the migration to be intermolecular.³⁴

3. Displacement of Sulfur

a. *By Ammonia and Amines.* Ammonia, at 80°C, transforms **12** ($R^1 = \text{Ar}$) into the amines **20** (Scheme 8)³⁵; the conversion has also been achieved at room temperature.²⁶ Hydrazine with **13** gives the corresponding derivatives



SCHEME 8

³³ F. Asinger, A. Saus, E. Fichtner, H. J. Gräber, and W. Leuchtenberger, *Monatsh. Chem.* **106**, 1449 (1975).

³⁴ F. Asinger, A. Saus, E. Fichtner, and W. Leuchtenberger, *Monatsh. Chem.* **106**, 1461 (1975).

³⁵ F. Asinger, W. Schäfer, and A. V. Grenacher, *Monatsh. Chem.* **96**, 741 (1965).

21 only when the ring substituents are bulky³⁰; otherwise tetrazines are formed. A wide range of primary and secondary aliphatic amines,^{25,36,37} as well as diamines,³⁷ react with **13**, forming the amines **22**; the reaction fails with arylamines.

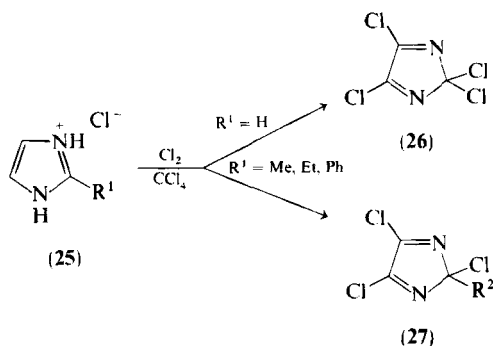
b. *By Alcohols.* In the presence of lead(II) oxide, primary and secondary alcohols convert **12** ($R^1 = \text{Ph}$) to the corresponding 5-alkoxy derivatives **23**³⁷; phenols do not react under these conditions.

c. *By Chlorine.* The iminochloride **24** is formed from **12** ($R^1 = \text{Ph}$) and sulfuryl chloride.³²

C. BY REACTION BETWEEN 1*H*-IMIDAZOLES AND ELECTROPHILES

1. Chlorination

Imidazolium salts **25** react with chlorine to yield chloro-2*H*-imidazoles **26** and **27** (Scheme 9).^{38,39} When $R^1 = \text{alkyl}$, $R^2 = \text{polychloroalkyl}$ in **27**. The action of phosphorus oxychloride on 2-ethylimidazole gives **27** ($R^2 = \text{CCl}_2\text{Me}$).⁴⁰ Some of the products have herbicidal action.^{41,42}



SCHEME 9

³⁶ F. Asinger, W. Schäfer, and G. Kriebel, *Monatsh. Chem.* **97**, 1108 (1966).

³⁷ F. Asinger, D. Neuray, A. Saus, J. Gräber, and U. Lames, *Monatsh. Chem.* **103**, 406 (1972).

³⁸ K. H. Büchel and H. Erdmann, *Chem. Ber.* **109**, 1625 (1976).

³⁹ K. H. Büchel and H. Erdmann, *Chem. Ber.* **109**, 1638 (1976).

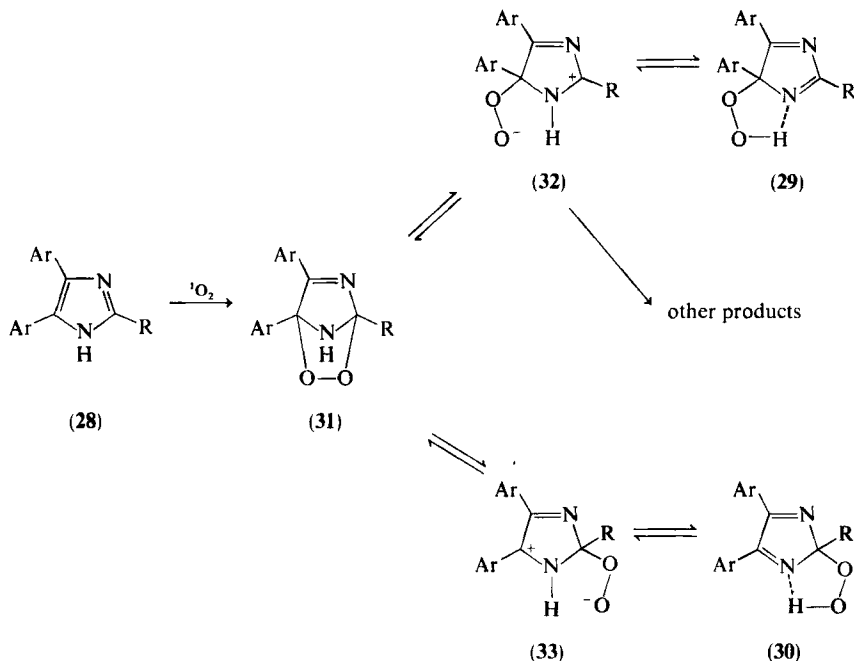
⁴⁰ G. Beck, H. Heitzer, and K. Luerssen, Ger. Offen. 2,550,157 (1977) [*CA* **87**, 85003 (1977)].

⁴¹ K. H. Büchel, Ger. Offen. 2,441,820 (1976) [*CA* **84**, 180223 (1976)].

⁴² G. Beck, H. Heitzer, L. Eue, and R. R. Schmidt, Ger. Offen. 2,901,862 (1980) [*CA* **94**, 65684 (1981)].

2. Photooxygenation

Addition of singlet oxygen (methylene blue sensitized) to 2,4,5-triarylimidazoles (**28**; R = aryl) (Scheme 10) has been known for some time to yield 4-hydroperoxy-4*H*-imidazoles (**29**).⁴³ It has been shown that at -15°C , under strictly dry conditions, the isomeric 2-hydroperoxy-2*H*-imidazoles (**30**) are formed,^{44,45} detectable by IR and ^1H -NMR spectroscopy when R = alkyl but not aryl. On standing at room temperature, compounds **30** change to **29** and other products.⁴⁵ Endoperoxides **31** are generally accepted to be the initial photoadducts⁴⁶; they have been identified by ^1H -NMR spectroscopy at -100°C for some imidazoles and observed in one case to change to a 2-hydroperoxy-2*H*-imidazole at -80°C .⁴⁷ The equilibria (Scheme 10) involving zwitterions **32** and **33** (or the corresponding diradicals⁴⁴) account



SCHEME 10

⁴³ J. Sonnenberg and D. M. White, *J. Am. Chem. Soc.* **86**, 5685 (1964); E. H. White and M. J. C. Harding, *ibid.*, 5686.

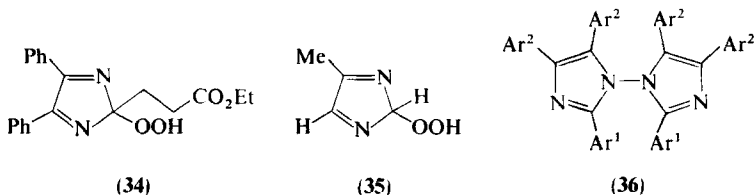
⁴⁴ M. L. Graziano, M. R. Iesce, and R. Scarpati, *J. C. S. Chem. Commun.*, 7 (1979).

⁴⁵ M. L. Graziano, G. Curato, and R. Scarpati, *J. Heterocycl. Chem.* **16**, 1571 (1979).

⁴⁶ H. H. Wasserman, M. S. Wolff, K. Stiller, I. Saito, and J. E. Pickett, *Tetrahedron* **37**, Suppl. 1, 191 (1981), and references cited therein.

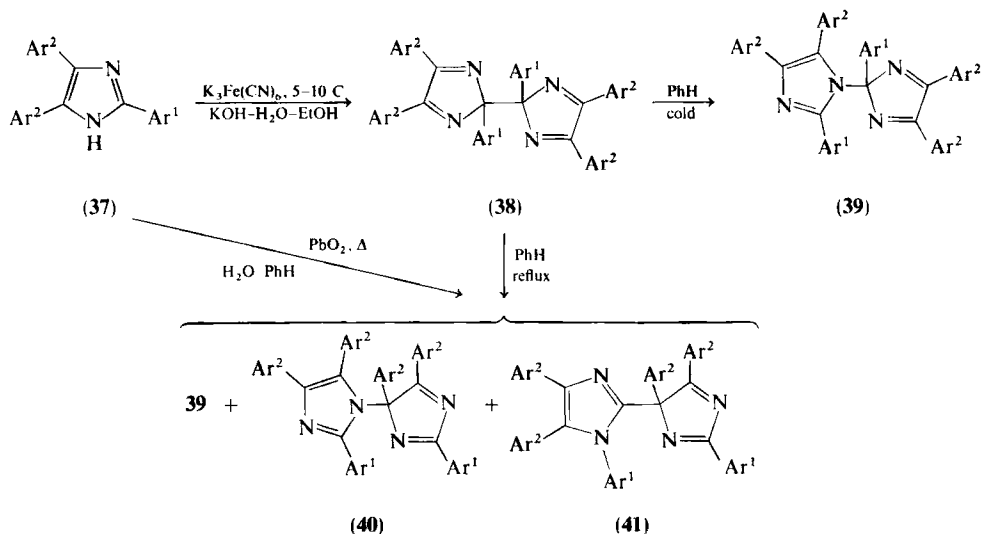
⁴⁷ H.-S. Ryang and C. S. Foote, *J. Am. Chem. Soc.* **101**, 6683 (1979).

for most experimental results (see also Section IV,A,1,b.); however, the products of this reaction depend heavily on temperature, solvent, and the nature of the ring substituents.^{45,46} Hydroperoxides **34**⁴⁶ and **35**⁴⁷ are unstable above -78°C .



3. Oxidative Dimerization

a. *Chemically.* The oxidation of triarylimidazoles gives a dimeric product, which was initially formulated as **36**⁴⁸⁻⁵⁰ and was observed to be photochromic, thermochromic, and piezochromic because of dissociation into triarylimidazolyl radicals. Later, the reaction was shown to be more complex (Scheme 11).



SCHEME 11

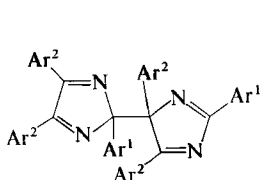
⁴⁸ T. Hayashi and K. Maeda, *J. Chem. Phys.* **32**, 1568 (1960); *Bull. Chem. Soc. Jpn.* **33**, 565 (1960); **35**, 2057 (1962).

⁴⁹ H. Zimmermann, H. Baumgärtel, and F. Bakke, *Angew. Chem.* **73**, 808 (1961); H. Baumgärtel and H. Zimmermann, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **18B**, 406 (1963) [*CA* **59**, 6382 (1963)].

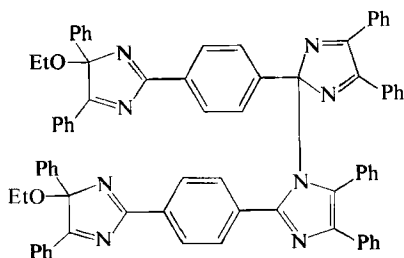
⁵⁰ H. Baumgärtel and H. Zimmermann, *Chem. Ber.* **99**, 843 (1966).

The initial product **38**, from aqueous basic potassium hexacyanoferrate(III) oxidation, was first formulated as the 4,4'-adduct⁵¹ and later corrected to the 2,2'-isomer on the basis of IR spectra,⁵² although it is still apparently given the 4,4'-structure in later papers. It is piezochromic, and it also rapidly isomerizes in solution in the cold, via the triarylimidazolyl radical, to the 1,2'-dimer **39**, which is both photo- and thermochromic.⁵¹⁻⁵³ The method of choice for preparing compounds **39**, which are important materials in photo- and thermocopying processes (Section IV,A,2), is to carry out the oxidation by using basic hexacyanoferrate(III) at room temperature in the presence of benzene.^{54,55}

Treatment of the sodium salts of **37** with an *N*-chloroimidazole,⁴⁹ or with bromine,^{49,50} also gives **39**. However, oxidation of **37** in refluxing benzene by lead(IV) oxide gives a mixture of three isomeric dimers (**39-41**), also obtainable from **38**⁵² (and **39**⁵⁶) in boiling benzene. Isomer **40**, whose structure has been confirmed as the 1,4'-dimer by two groups,^{52,53} like **39** is both photo- and thermochromic. The nature of the third isomer is less certain, having been assigned as **42** on the basis of ¹H-NMR spectra,^{52,56} as **41** (for Ar = Ph) from a cyclic voltammogram,⁵³ and as **40** from a comparison of ¹³C-NMR spectra with those of model compounds.⁵⁷ Of these, **41** seems the most likely because the isomer is thermochromic but not photochromic, suggesting a C—C linkage.^{53,56} Further, the ¹³C-NMR spectrum, assigned as structure **40**, is also consistent with **41** but not **42**.⁵⁷ An X-ray crystal structure determination would be useful.



(42)



(43)

⁵¹ D. M. White and J. Sonnenberg, *J. Am. Chem. Soc.* **88**, 3825 (1966).

⁵² H. Tanino, T. Kondo, K. Okada, and T. Goto, *Bull. Chem. Soc. Jpn.* **45**, 1474 (1972).

⁵³ U. Lang and H. Baumgärtel, *J. Electroanal. Chem. Interfacial Electrochem.* **78**, 133 (1977).

⁵⁴ L. A. Cescon, G. R. Coraor, R. Dessauer, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.* **36**, 2262 (1971).

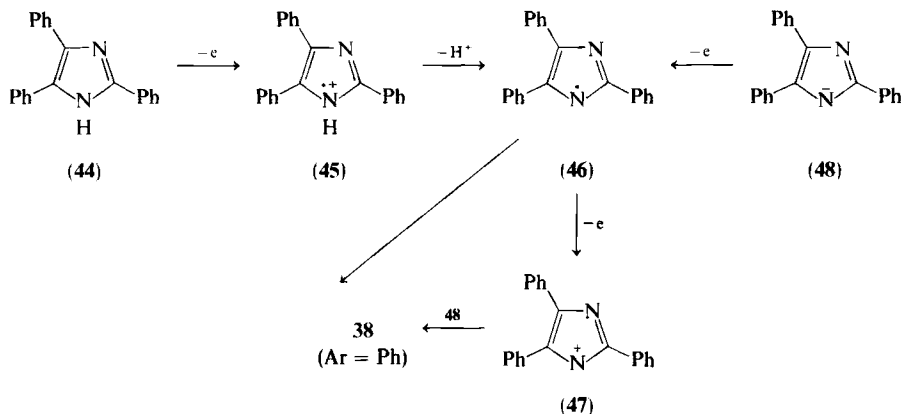
⁵⁵ L. A. Cescon, U.S. Patent 3,784,557 (1974) [*CA* **80**, 82976 (1974)].

⁵⁶ T. Goto, H. Tanino, and T. Kondo, *Chem. Lett.*, 431 (1980).

⁵⁷ G. Domany, J. Nyitrai, K. Lempert, W. Voelter, and H. Horn, *Chem. Ber.* **111**, 1464 (1978).

The dimer **43**, which is piezo-, photo-, and thermochromic, is formed together with two 4*H*-imidazole products on hexacyanoferrate(III) oxidation of a *p*-phenylene-bis-1*H*-imidazole precursor.⁵⁸

b. *Electrochemically.* The 2,2'-dimer **38** is also reported to be the product from electrochemical oxidation of 2,4,5-triphenylimidazole (**44**, Scheme 12) in acetonitrile, using a rotating platinum electrode.⁵⁹ Reduction proceeds via the radical cation **45**, and by deprotonation, to the radical **46**; this dimerizes to **38** (Ar = Ph), although it is the rearranged isomer **39** that is isolated. Further oxidation of **46** to cation **47** has also been achieved, both from **44**⁵⁹ and from anion **48**.⁵³ Dimers are formed in a reaction between **47** and **48**, which proceeds very much more rapidly than radical (**46**) combination.⁵³



SCHEME 12

D. MISCELLANEOUS METHODS

1. From Azirines

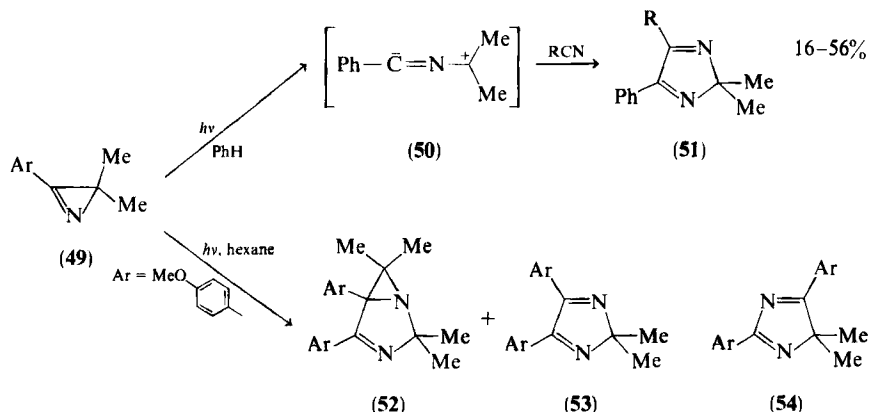
a. *Photochemically.* The azirine **49** (Ar = Ph, Scheme 13) on photolysis in benzene opens to a nitrile ylide (**50**), which may be trapped with electron-deficient nitriles via a 1,3-dipolar cycloaddition to give 2*H*-imidazoles (**51**).⁶⁰ The reaction is regiospecific, no 4*H* isomers being formed.

In hexane and in the absence of an added trapping agent, **49** (Ar = 4-MeOC₆H₄) yields the bicycle **52**, apparently by cycloaddition between the

⁵⁸ Y. Sakaino, H. Kakisawa, T. Kusumi, and K. Maeda, *J. Org. Chem.* **44**, 1241 (1979).

⁵⁹ M. Libert and C. Cautlet, *Bull. Soc. Chim. Fr.*, 345 (1976).

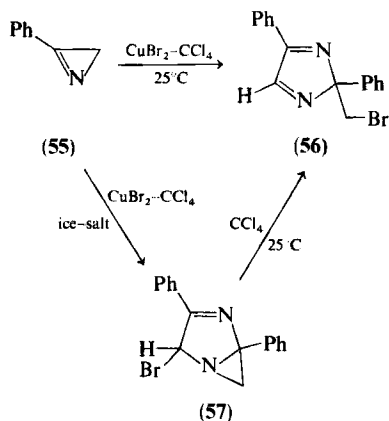
⁶⁰ W. Stegmann, P. Gilgen, H. Heimgartner, and S. H. Schmid, *Helv. Chim. Acta* **59**, 1018 (1976).



SCHEME 13

nitrile ylide and unreacted azirine, along with what is claimed to be **53**.⁶¹ However, the two aryl methoxy groups in the latter are reported to have different chemical shifts (δ 3.67 and 3.75); the product may thus be the *4H* isomer **54**.

b. *Thermally.* Treatment of **55** (Scheme 14) with copper(II) bromide in carbon tetrachloride at room temperature leads to **56**. At lower temperatures, the intermediate bicycle **57** can be isolated; it is converted to **56** in solution at room temperature.⁶²



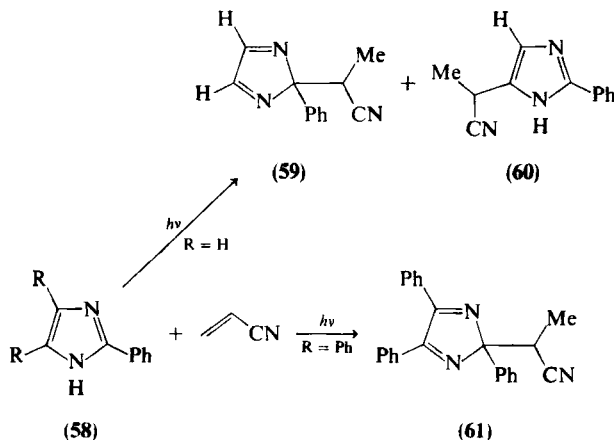
SCHEME 14

⁶¹ U. Gerber, H. Heimgartner, H. Schmid, and W. Heinzelmann, *Helv. Chim. Acta* **60**, 687 (1977).

⁶² K. Hayashi, K. Isomura, and H. Taniguchi, *Chem. Lett.*, 1011 (1975).

2. From 1H-Imidazoles and Propenenitrile

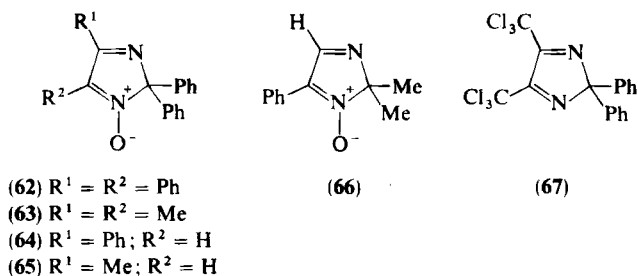
Photolysis of **58** ($R = H$, Scheme 15) in ethanol or acetonitrile, in the presence of excess propenenitrile, yields small amounts of **59** together with **60**. When $R = Ph$ (**44**), the product is **61** (34–38%).⁶³



SCHEME 15

3. From 2H-Imidazole N-Oxides

Reduction of **62** by lithium aluminum hydride in hot dioxane,⁶⁴ or by hexachlorodisilane in chloroform,¹² gives **7**; the latter reagent likewise converts **63** and **66** to the corresponding 2H-imidazoles.¹² 2H-Imidazoles are also formed by sodium borohydride reduction of **64** and **65**, although this reagent has no effect on **62** and **63**.⁶⁴



⁶³ Y. Ito and T. Matsuura, *Tetrahedron Lett.*, 513 (1974); *J. Org. Chem.* **44**, 41 (1979).

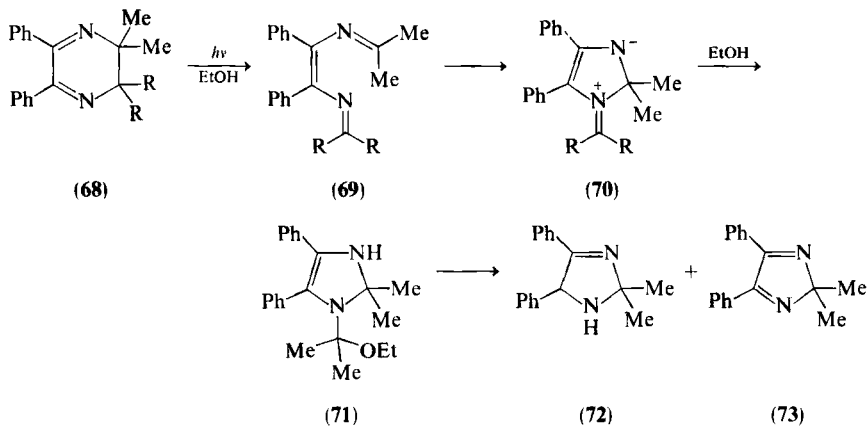
⁶⁴ B. A. J. Clark, T. J. Evans, and R. G. Simmonds, *J. C. S. Perkin I*, 1803 (1975).

4. From Diphenyldiazomethane and a Nitrile

Reaction between trichloroacetonitrile and Ph_2CN_2 at low temperatures yields **67**; other electron-deficient nitriles give different products.⁶⁵ It is possible that the reaction proceeds via an unstable $3H$ -1,2,4-triazole intermediate, which loses N_2 to form a nitrile ylide before adding a second mole of nitrile as in Scheme 13.

5. From Dihydropyrazines

Photolysis of **68** ($\text{R} = \text{Me}$; high-pressure Hg lamp) in absolute ethanol leads to **72** (60%) and **73** (9%), the reaction being presumed to go via the ring-opened enediimine **69** (Scheme 16). It was suggested that **73** might arise from photooxidation of **72**, which in turn could be formed from **71** with concomitant production of 2,2-diethoxypropane.⁶⁶ An enediimine (**69**; $\text{R} = \text{H}$) has subsequently been characterized in a hydrocarbon-xenon matrix at 63 K, from photolysis of the corresponding **68**⁶⁷; further, the observed photochemical reduction of **73** to **72** in isopropanol suggests that the $2H$ -imidazole is a precursor to **72** and not a by-product.⁶⁷



SCHEME 16

E. METHODS FOR N -OXIDES

Most routes make use of noncyclic precursors, although there have been two reports involving direct oxidation of $2H$ -imidazoles.

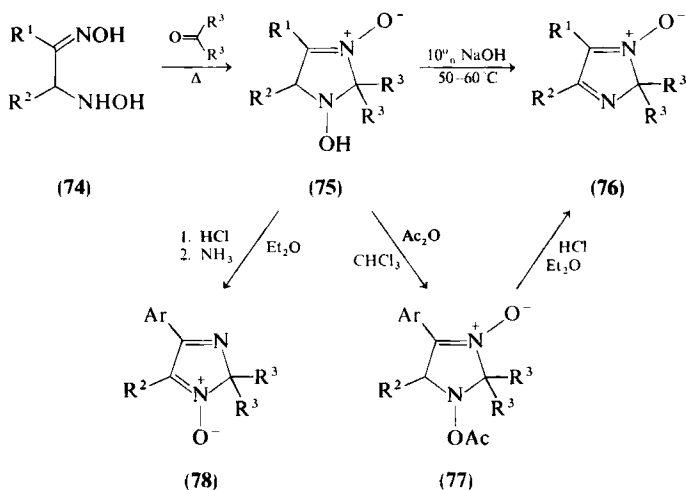
⁶⁵ G. F. Bettinetti, A. Donetti, and P. Grünanger, *Tetrahedron Lett.*, 2933 (1966).

⁶⁶ P. Beak and J. L. Miesel, *J. Am. Chem. Soc.* **89**, 2375 (1968).

⁶⁷ D. R. Arnold, V. Y. Abraitys, and D. McLeod, Jr., *Can. J. Chem.* **49**, 923 (1971).

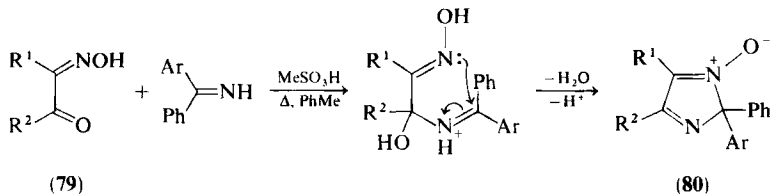
1. *N*-Oxides

a. *From Noncyclic Precursors.* α -Hydroxyimino oximes **74** ($R^1, R^2 =$ alkyl; Scheme 17) react with propanone to give the imidazolines **75**, which on reaction with sodium hydroxide are converted to the *N*-oxides **76** ($R^3 =$ Me).⁶⁸ When $R^1 = \text{Ar}$, acetylation of **75** yields **77**, which on reaction with hydrogen chloride also gives **76**.⁶⁹ However, when **75** ($R^1 = \text{Ar}$) is treated with dry hydrogen chloride and then ammonia, the isomeric *N*-oxides **78** are isolated.⁶⁹



SCHEME 17

The more accessible α -hydroxyimino ketones **79** (Scheme 18) undergo an acid-catalyzed condensation with diarylimines to yield the *N*-oxides **80** (30–80%).⁶⁴



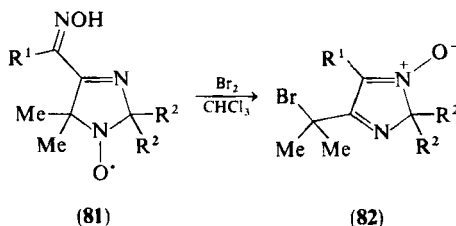
SCHEME 18

⁶⁸ Y. G. Putsykin and L. B. Volodarskii, *Dokl. Akad. Nauk SSSR* **4**, 86 (1964); *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 86 (1969) [*CA* **72**, 54514 (1970)].

⁶⁹ L. B. Volodarskii, A. N. Lysak, and V. A. Koptiyug, *Khim. Geterotsikl. Soedin.*, 334 (1968) [*CA* **69**, 96577 (1968)].

Thermal cyclization–rearrangement of *N*-nitroso-3-methyl-2-phenyl-2-butenaldimine has been reported to yield **76** ($R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Me}$) as one of several products.¹²

The nitroxyls **81** (Scheme 19) on bromination rearrange to the bromo *N*-oxides **82**.⁷⁰

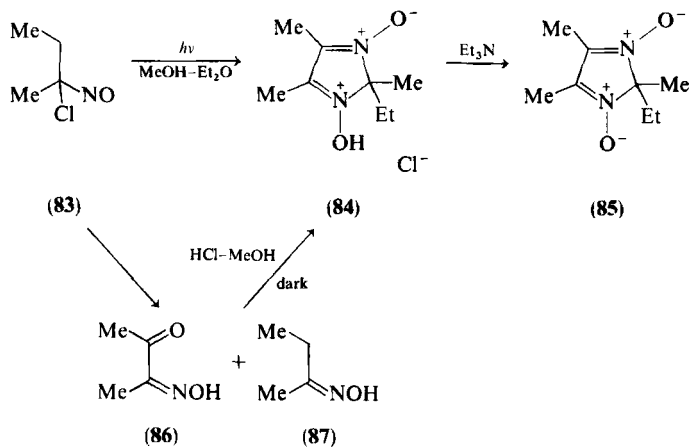


SCHEME 19

b. *By Oxidation of 2H-Imidazoles.* *m*-Chloroperbenzoic acid (MCPBA) in dichloromethane converts **7** to **62** (40%).⁶⁴

2. *N,N'*-Dioxides

a. *From Noncyclic Precursors.* Photolysis of **83** in methanol gives **84**, convertible by base to the dioxide **85** (Scheme 20). The reaction is believed to proceed via fragments **86** and **87** in as much as these combine in the

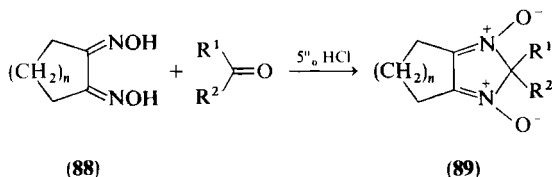


SCHEME 20

⁷⁰ G. I. Shchukin, I. A. Grigor'ev, and L. B. Volodarskii, *Izv. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1581 (1981) [*CA* **95**, 187150 (1981)].

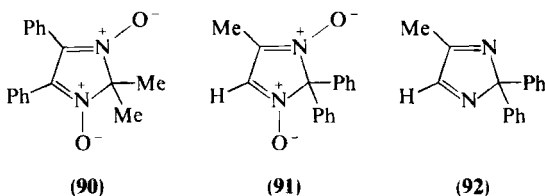
presence of hydrogen chloride to form **84**.⁷¹ The monohydrate of **85** had been prepared earlier but identified incorrectly as having an open-chain structure.⁷²

Cyclic 1,2-dioximes **88** ($n = 2, 3$; Scheme 21) yield dioxides **89** ($R^1, R^2 = \text{alkyl}$, 32–60%) on reaction with ketones.^{73,74}



SCHEME 21

b. *By Oxidation of 2H-Imidazoles.* Hydrogen peroxide (30%) in acetic acid converts **73** to **90** (88%) at room temperature; the 2,2-diethyl analog is prepared similarly.¹¹ A small amount of **91**, together with an imidazolone, was isolated from MCPBA oxidation of **92**.⁶⁴



F. N-YLIDES

Photolysis^{75–77} or thermolysis^{77,78} of the bicycles **93** give intensely colored intermediates that are relatively stable at low temperatures. These appear to be the *N*-ylides **94** (Scheme 22), formed apparently from a conrotatory ring-opening process from the ground state.⁷⁷ They have been trapped by a number of dipolarophiles (see Section IV,D,2).

⁷¹ J. E. Baldwin and N. H. Rogers, *J. C. S. Chem. Commun.*, 524 (1965).

⁷² S. Mitchell and J. Cameron, *J. Chem. Soc.*, 1964 (1938).

⁷³ L. B. Volodarskii and V. A. Samsonov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 971 (1978) [*CA* **89**, 24220 (1978)].

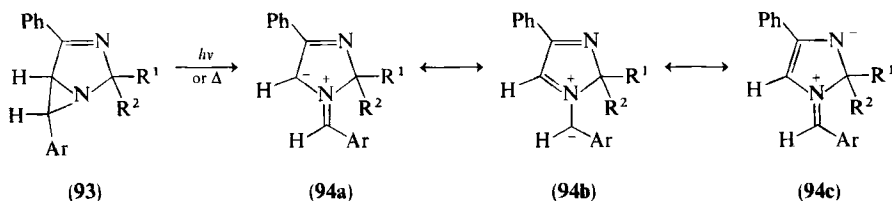
⁷⁴ V. A. Samsonov and L. B. Volodarskii, *Khim. Geterotsikl. Soedin.*, 808 (1980) [*CA* **93**, 186242 (1980)].

⁷⁵ A. Padwa, S. Clough, and E. Glazer, *J. Am. Chem. Soc.* **92**, 1778 (1970).

⁷⁶ Thap DoMinh and A. M. Trozzolo, *J. Am. Chem. Soc.* **92**, 6997 (1970).

⁷⁷ Thap DoMinh and A. M. Trozzolo, *J. Am. Chem. Soc.* **94**, 4046 (1972).

⁷⁸ H. W. Heine, A. B. Smith, III, and J. D. Bower, *J. Org. Chem.* **33**, 1097 (1968).



SCHEME 22

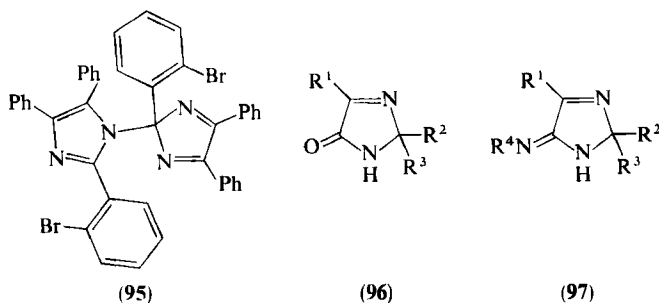
Similar structures appear to be intermediates in the photolysis of dihydropyrazines (Scheme 16),^{66,67,79} and are also formed from the base treatment of certain *N*-methyl-2*H*-imidazolium salts (Section IV,D,2).¹¹

III. Structure and Physical Properties

A. STRUCTURE

1. X-Ray Crystallography

It has been reported that no two rings in the biimidazole **95** are coplanar because of steric crowding,⁵⁴ but no details have been published.



2. Tautomerism

No MO calculations appear to have been carried out to compare the relative stabilities of simple 1*H*-, 2*H*-, and 4*H*-imidazoles. However, **35** is claimed to be kinetically stable at low temperatures,⁴⁷ and MNDO calcula-

⁷⁹ D. L. Kleyer and T. H. Koch, *J. Org. Chem.* **47**, 3145 (1982).

tions have suggested that for some amino-substituted imidazoles the 2*H* (and 4*H*) forms can be more stable than the 1*H* form.⁸⁰

Spectroscopic evidence shows that structures **96**⁶⁴ and **13**³¹ are the correct formulations, the latter being irrespective of the solvent. Amino derivatives appear to exist as, e.g., **20** and **21**, rather than the alternative forms **97**.^{25,26,30} Of the eight possible tautomers of the parent imidazolin-5-one, including 2*H*- and 4*H*-imidazole forms, CNDO/2 and PCILO calculations show Δ^2 -imidazolin-5-one to be the most stable,⁸¹ as is observed in practice.

B. SPECTROSCOPIC DATA

1. Ultraviolet Spectra

Structure **59**, which has no conjugating substituents, absorbs in ethanol at 240 nm ($\log \epsilon$ 3.06), with weaker shoulders between 259 and 269 nm.⁶³ Introduction of one⁶⁰ or two^{53,57,60,67} conjugating aryl groups shifts the principal absorption to 261–276 nm ($\log \epsilon$ 3.71–3.97). A change of solvent from ethanol to hydrocarbons results in a small hypsochromic shift and an increase in $\log \epsilon$.^{12,67} In some spectra, a weak, long wavelength band (280–290 nm) has been reported.^{12,21} For biimidazoles **39** ($\text{Ar}^2 = \text{Ar}^3 = \text{Ph}$) absorption is in the narrow range 262–267 nm ($\log \epsilon$ 4.40–4.59) regardless of the nature or position of the substituent on Ar^1 , showing that Ar^1 is rotated out of the plane of the 1*H*-imidazole ring,⁵⁴ consistent with X-ray data for **95**.

No UV data appear to have been reported for mono-*N*-oxides; the *N,N*-dioxide **85** has a peak at 347 nm ($\log \epsilon$ 3.98).⁷¹

N-Ylides **94** ($\text{Ar} = 4\text{-NO}_2\text{C}_6\text{H}_4$) absorb near 600 nm at 77 K, the peak shifting to longer wavelength by 20–30 nm at 298 K.⁷⁷

2. Infrared Spectra

Simple tetraalkyl-2*H*-imidazoles show a peak near 1575 cm^{-1} , arising from the $\text{C}\equiv\text{N}$ bond.¹³ In aryl-substituted compounds, a characteristic band near 1615 cm^{-1} has been identified,⁸² and confirmed between 1600 and 1620 cm^{-1} by other authors.^{11,44,45,62} In 2*H*-imidazolium salts, it falls

⁸⁰ R. Gompper, M. Junius, and H.-U. Wagner, *Tetrahedron Lett.*, **22**, 2973 (1981).

⁸¹ A. Sayarh, M. Gelize-Duvigneau, J. Arriau, and A. Maquestiau, *Bull. Soc. Chim. Belg.* **88**, 289 (1979).

⁸² D. M. White and J. Sonnenberg, *J. Org. Chem.* **29**, 1926 (1964).

in the same range.¹¹ A common intense absorption near 1490 cm^{-1} has been assigned both to the 2*H*-imidazole ring⁶⁰ and to phenyl substituents.⁸²

2-Hydroperoxy compounds **30** ($\nu_{\text{O-O}} \approx 860\text{ cm}^{-1}$) show evidence of an intramolecular H bond ($\nu_{\text{OH}} 2820\text{ cm}^{-1}$); the corresponding 2-hydroxy compounds absorb near 3600 cm^{-1} .^{44,45}

For a series of 2,2-diaryl *N*-oxides $\nu_{\text{C=N}}$ and $\nu_{\text{N-O}}$ have been correlated respectively with bands in the ranges $1560\text{--}1619$ and $1120\text{--}1180\text{ cm}^{-1}$.⁶⁴ Both symmetric (1520 cm^{-1}) and antisymmetric (1570 , 1590 cm^{-1}) C=N modes have been assigned in two isomeric 2,2-dimethyl *N*-oxides; the latter were inactive in the laser Raman spectra.⁸³

The *N,N'*-dioxide **85** absorbs between 1560 and 1580 cm^{-1} .⁷¹

3. ¹H-Nuclear Magnetic Resonance Spectra

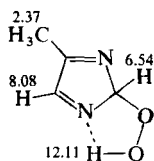
Only one compound (**35**) having a proton at the 2-position is known; the signal at 193 K is at δ 6.54.⁴⁷ Protons at the 4- and 5-positions give signals in the range δ 7.98–8.57 (e.g., **35**, **59**, **92**, **98**, and **99**).^{12,47,62–64} One example (**59**), in which two such ring protons are rendered diastereotopic by a chiral 2-substituent, shows coupling $^3J_{\text{HH}} = 5.5\text{ Hz}$.⁶³ Coupling $^4J_{\text{HH}}$ is not apparently observed between 4-Me and 5-H substituents.^{47,64}

2-Methyl group signals are generally found in the range δ 1.56–1.70 when 4- and 5-aryl groups are present (e.g., **73** and **98**),^{10–12,60,67} but at higher field (**100**) in the absence of aryl substituents.¹³ Methyls at the 4- and 5-positions appear between δ 2.3 and 2.5 (e.g., **35**, **92**, **100**, and **101**).^{12,13,44,45,47,64}

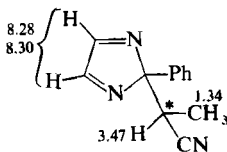
Protons on 2-hydroxy groups fall in the range δ 5.8–6.2, whereas the intramolecularly H-bonded 2-hydroperoxy proton signals appear between δ 11.85 and 12.30.^{44,45,47}

Quaternization of the 2*H*-imidazole ring results in the expected down-field shift of methyl signals (e.g., **102**).¹¹

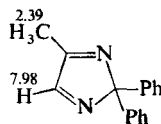
Some examples (**65**, **91**, **90**) of the few reported^{11,64,71} *N*-oxide spectra are illustrated.



(35)

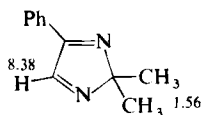


(59)

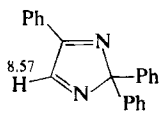


(92)

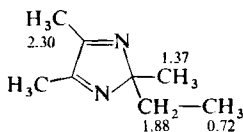
⁸³ I. K. Korobeinicheva, M. M. Mitasov, V. S. Kobrin, and L. B. Volodarskii, *Izv. Sib. Otd. Nauk SSSR, Ser. Khim. Nauk*, 96 (1976) [*CA* **85**, 26913 (1976)].



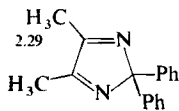
(98)



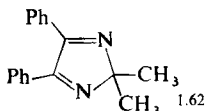
(99)



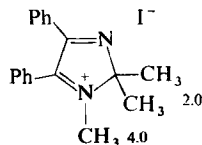
(100)



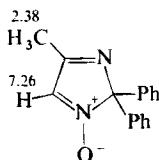
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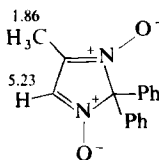
(73)



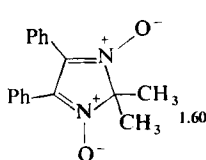
(102)



(65)



(91)



(90)

4. ^{13}C -Nuclear Magnetic Resonance Spectra

For ring carbon atoms, the signal for C-2 has been found to range from δ 101 to 119 (101.34 in **73**) and for C-4 and C-5 from δ 158 to 165 (163.70 in **73**).^{38,44,57,60} Methyl substituents at C-2 absorb near δ 24.^{44,60}

5. Mass Spectra

Most 2*H*-imidazoles show a parent ion that can be quite prominent.^{12,60,62,64,84} The major fragmentation pathway involves loss of RCN (two possible ways when the C-4 and C-5 substituents are different) and often gives rise to the base peak. Thus the 4-phenyl compounds show a prominent $M^+ - 103$ ion, and structures **51** a common peak at m/e 145 ($M^+ - \text{RCN}$).^{12,60}

The tetraphenyl compound **7** has a mass spectrum essentially the same as the 4*H*, but quite different from the 1*H* isomer.⁸⁴

Neither *N*-oxides⁶⁴ or *N,N'*-dioxides¹¹ show the intense $M - 16$ or $M - 17$ peaks often associated with heterocyclic *N*-oxides⁸⁵; the former give a prominent parent ion.⁶⁴

⁸⁴ G. Domany and J. Nyitrai, *Acta Chim. Acad. Sci. Hung.* **90**, 109 (1976) [*CA* **86**, 72522 (1977)].

⁸⁵ A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides," p. 17. Academic Press, New York, 1971.

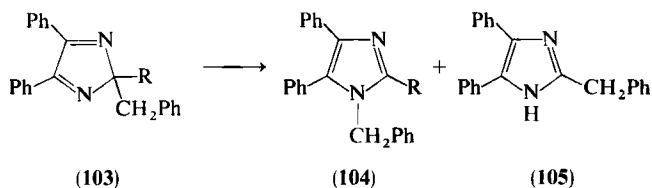
IV. Reactions of 2*H*-Imidazoles

A. THERMAL AND PHOTOCHEMICAL REACTIONS FORMALLY INVOLVING NO OTHER SPECIES

1. Thermal Reactions of Mononuclear Compounds

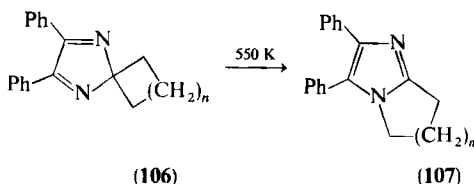
As is the case with 2*H*- and 3*H*-pyrroles,¹ and with 3*H*- and 4*H*-pyrazoles,² the 2*H*-imidazoles undergo both thermal and acid-catalyzed rearrangements. The products may be 1*H*- or 4*H*-imidazoles, depending on the ring substituents.

a. *Rearrangements to 1*H*-Imidazoles.* Weiss observed that **103** (R = PhCH₂) rearranged to **104** (R = PhCH₂) at 250°C and to a mixture of **104** and **105**, which were not interconvertible, in boiling methanoic acid (Scheme 23).⁸ Further, **7** gave 1,2,4,5-tetraphenylimidazole at 300°C, whereas an attempt to prepare **103** (R = Ph) from benzil and 1,2-diphenylethanone yielded only the corresponding **104** under the (acidic) reaction conditions.⁸



SCHEME 23

A more detailed kinetic study showed that migratory aptitudes of 2-substituents in 4,5-diphenyl-2*H*-imidazoles were in the order Me < Et < Ph < PhCH₂; further for the spiro compounds **106**, rearrangement to **107** (Scheme 24) occurred during preparation of **106** (*n* = 1), and with a rate extending over three orders of magnitude for *n* = 2–9.¹⁰ Activation energies *E*_a for a series of migrations were in the range 157–207 kJ/mol, whereas Δ*S*[‡] ranged from +46 to –29 J/mol/K, the latter being consistent with a concerted intramolecular process. This was confirmed by crossover and

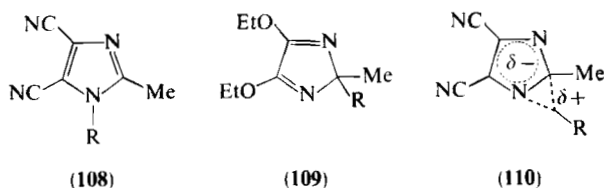


SCHEME 24

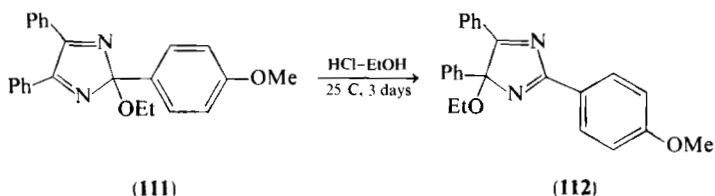
radical-trapping experiments.¹⁰ Rates varied little in different solvents and in melts. For 2,2-di(*p*-substituted) benzyl derivatives, a plot of $\log k$ against σ^+ gave $\rho = -1.15$, again suggesting a concerted mechanism, but with some charge development in the transition state.¹⁰

For thermal rearrangements of **9** to **108**, migratory aptitudes for R were $\text{Me} < \text{Et} \approx n\text{Pr} < i\text{Pr}$; in contrasts, **109** did not rearrange.²¹ The authors proposed an intermediate **110**, stabilized by the 4- and 5-substituents.

Thermolysis of **59** and **61** caused some reversion to **58**.⁶³

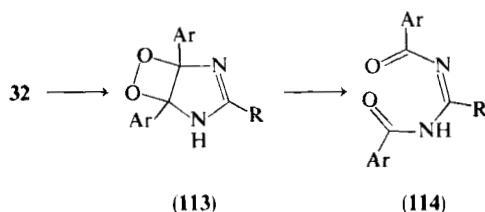


b. *Rearrangements to 4H-Imidazoles.* Ethoxy compounds **111** are converted to **112** in an acid-catalyzed reaction (Scheme 25).⁵² This, and the rearrangement in Scheme 10, suggests that 4H-imidazoles having an oxy substituent at the tetrahedral carbon atom are thermodynamically more stable than their 2H counterparts.



SCHEME 25

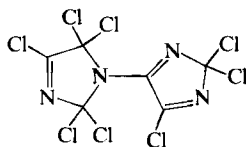
The interconversion of **30** to **29** via the intermediate **32** (Scheme 10) also results in the formation of a dioxetane **113**, which gives **114** by a chemiluminescent reaction, especially in the presence of base (Scheme 26).^{43,44,46} An N-substituted analog of **113** has been isolated.⁸⁶



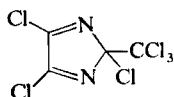
SCHEME 26

⁸⁶ G. Rio and B. Serkiz. *J. C. S. Chem. Commun.*, 849 (1975).

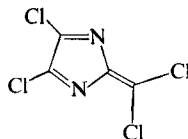
c. *Other Reactions.* The pentachloro compound **26**, on heating with maleic anhydride, yields the dimer **115** and not a Diels–Alder adduct.^{38,41} Thermal loss of chlorine from **116** gives the diazafulvene **117**.⁸⁷



(115)



(116)

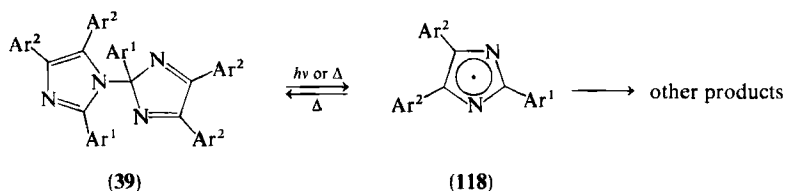


(117)

2. Thermal and Photochemical Rearrangements of Biimidazoles

As discussed in Section II,C,3, hexaarylbiimidazoles **38** are unstable, rearranging to **39** in cold solvents,^{51–53} or to a mixture of **39–41** in refluxing benzene.⁵² Further, each isomer **39**, **40**, or **41** is converted individually to the same equilibrium mixture of all three (ratio 14:18:68) at 100°C; however, **39** and **40** on irradiation (high-pressure Hg lamp) individually give the same equilibrium mixture of the two (96:4; **41** is not formed).⁵⁶ Isomer **41** must arise from a thermal sigmatropic rearrangement of **39** or **40**, perhaps via **42**. Above 200°C, the N,N-linked dimer **36** is formed⁵⁷; this finds a parallel in a thermal rearrangement of a 2,2'-bis-2*H*-pyrrole to the 1,1'-isomer.⁸⁸

Rearrangement reactions of biimidazoles proceed through triarylimidazolyl radicals **118**,^{48,51} which have been detected by ESR.⁴⁸ The most extensively studied reaction has been the reversible conversion of **39** to **118** (Scheme 27), and it has been recommended as an undergraduate experi-



SCHEME 27

⁸⁷ G. Beck, F. Doering, H. Heitzer, and H. Holtschmidt, Ger. Offen. 2,454,326 (1976) [CA **85**, 63071 (1976)].

⁸⁸ M. R. C. Gerstenberger, A. Haas, B. Kirste, C. Krüger, and H. Kurreck, *Chem. Ber.* **115**, 2540 (1982).

ment.⁸⁹ The kinetics have been followed for the photo⁹⁰ and the thermal^{49,50,91} dissociation of **39** in solution and for the recombination of **118**, generated by flash photolysis, to **39**.^{54,92,93} Thermal and photochemical dissociation and recombination have also been investigated in a solid polymer phase.⁹⁴ Thermodynamic parameters have been evaluated in a number of solvent systems and for a range of aryl substituents.^{49,50,90-92}

Radical decay kinetics have been shown to be 3/2 order, falling to first order,⁹² and also second order, falling with time⁵⁴; deviations are apparently due to side reactions of **118**. Radical half-lives are strongly influenced by the nature of the aryl substituents, being particularly short for ortho-substituted Ar¹ because of inhibited delocalization. The corresponding compounds **39** have, accordingly, enhanced thermal stability,⁵⁴ a factor useful in some commercial thermo- and photographic processes.

The ability of the radical **118** thermally or photochemically generated from **39** to combine with other substrates to generate permanently colored species⁹⁵ has found wide use in color image copying.^{55,96}

B. REACTIONS OF RING ATOMS WITH ELECTROPHILES

1. Salt Formation

No simple hydrosalts of 2H-imidazoles appear to have been reported. Whereas **103** (R = PhCH₂) was cleaved quantitatively to **105** and benzyl chloride in hot hydrochloric acid,⁸ other 2H-imidazoles underwent ring cleavage to give ketones or products derived from them (e.g., **119**, Scheme 28).^{8,29,62,63}

⁸⁹ M. Pickering, *J. Chem. Educ.* **57**, 833 (1980).

⁹⁰ A. L. Prokhoda and V. A. Krongauz, *Khim. Vys. Energ.* **5**, 262 (1971) [*CA* **75**, 56776 (1971)].

⁹¹ B. S. Tanaseichuk, A. I. Belozerov, L. G. Tikhonova, V. N. Shishkin, A. A. Bardina, and K. P. Butin, *Zh. Org. Khim.* **14**, 2029 (1978) [*CA* **90**, 103025 (1978)].

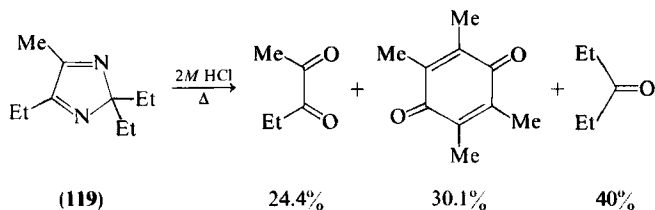
⁹² M. A. J. Wilks and M. R. Willis, *J. Chem. Soc. B*, 1526 (1968).

⁹³ A. L. Prokhoda and V. A. Krongauz, *Khim. Vys. Energ.* **3**, 495 (1969) [*CA* **72**, 42499 (1970)].

⁹⁴ G. Smets, G. Nijst, M. Schmitz-Smets, and A. Somers, *J. Polym. Sci., Polym. Symp.* **67**, 83 (1980) [*CA* **94**, 104194 (1980)].

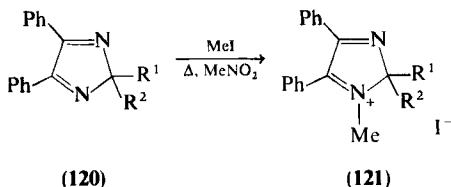
⁹⁵ L. A. Cescon, G. R. Coraor, R. Dessauer, A. S. Deutsch, H. L. Jackson, A. MacLachlan, K. Marcali, E. M. Potrafke, R. E. Read, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.* **36**, 2267 (1971); R. H. Riem, A. MacLachlan, G. R. Caraor, and E. J. Urban, *ibid.*, 2272; A. MacLachlan and R. H. Riem, *ibid.*, 2275; R. L. Cohen, *ibid.*, 2280.

⁹⁶ D. S. James and V. G. Witterholt, U.S. Patent 3,533,797 (1970) [*CA* **74**, 48080 (1971)]; L. A. Cescon and R. Dessauer, U.S. Patent 3,585,038 (1971) [*CA* **75**, 82384 (1971)]; C. E. Looney, U.S. Patent 3,615,481 (1971) [*CA* **76**, 29536 (1971)]; H. Gerlach, Jr. and C. E. Looney, Ger. Offen 2,162,671 (1972) [*CA* **77**, 146258 (1972)]; C. J. Fox, U.S. Patent 3,765,895 (1973) [*CA* **81**, 8436 (1974)]; R. Dessauer and C. E. Looney, U.S. Patent 3,909,328 (1975) [*CA* **84**, 24434 (1976)]; R. Dessauer, U.S. Patent 4,029,506 (1977) [*CA* **87**, 93580 (1977)].



SCHEME 28

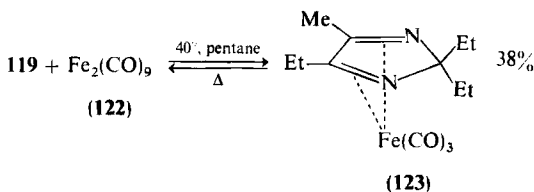
4,5-Diphenyl-2*H*-imidazoles **120** have been shown to form methosalts **121** in high yields (Scheme 29); ethyl iodide, however, gave only small amounts of ethosalts.¹¹ In 4-amino compounds, methylation occurs at the ring N-3.³⁵



SCHEME 29

2. Complex Formation

Complex **123** is formed reversibly between **119** and **122** (Scheme 30); this has been proposed as an excellent method for purifying 2*H*-imidazoles free from precursors.⁹⁷



SCHEME 30

3. Oxidation by Peracids

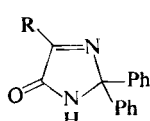
The peracid oxidation of 2*H*-imidazoles to *N*-oxides and *N,N'*-dioxides has been discussed (Section II,E); both **92** and **99** under similar conditions give imidazolinones **124**.⁶⁴

⁹⁷ H. tom Dieck and H. Bock, *J. C. S. Chem. Commun.*, 678 (1968).

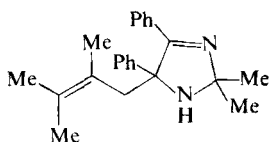
C. REACTIONS OF RING ATOMS WITH NUCLEOPHILES

1. Reducing Agents

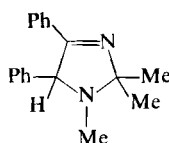
a. *Photochemical Reduction.* Although **73** is unaffected by irradiation in hexane, it is reduced to **72** in 2-propanol (medium-pressure Hg lamp).⁶⁷ In a related reaction, **125** is formed in 2,3-dimethyl-2-butene.⁶⁷



(124)



(125)

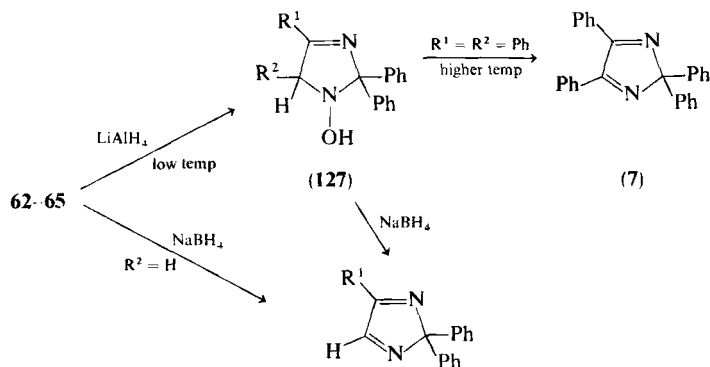


(126)

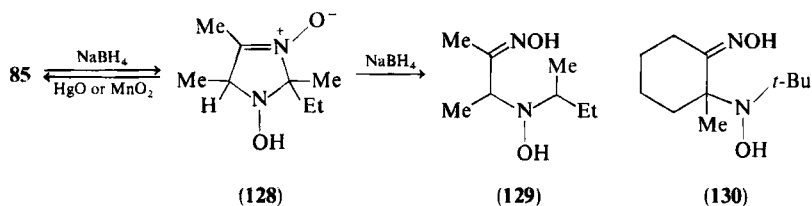
b. *Catalytic Hydrogenation.* The free base **73** is reduced to **72** at 50 psi over palladium,⁶⁴ whereas **26** is converted quantitatively to 2,4,5-trichloro-1*H*-imidazole over platinum oxide.³⁸

c. *Metal Hydrides.* The biimidazoles **38** and **39** ($\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$), upon treatment with lithium aluminum hydride, both give **44**⁵¹; compounds **59** and **61** are also reduced to **58**.⁶³ Sodium borohydride, even in excess, reduces **102** only as far as **126**.¹¹

The behavior of *N*-oxides depends both on the substituents and on the reducing agent (Scheme 31)⁶⁴; sodium borohydride has no effect on **62** or **63**. *N,N'*-Dioxides may be reduced in two stages (e.g., **128** and **129**, Scheme 32)⁷¹; for **89** ($n = 2$; $\text{R}^1 = \text{R}^2 = \text{Me}$), only the first product was isolated.⁷³



SCHEME 31



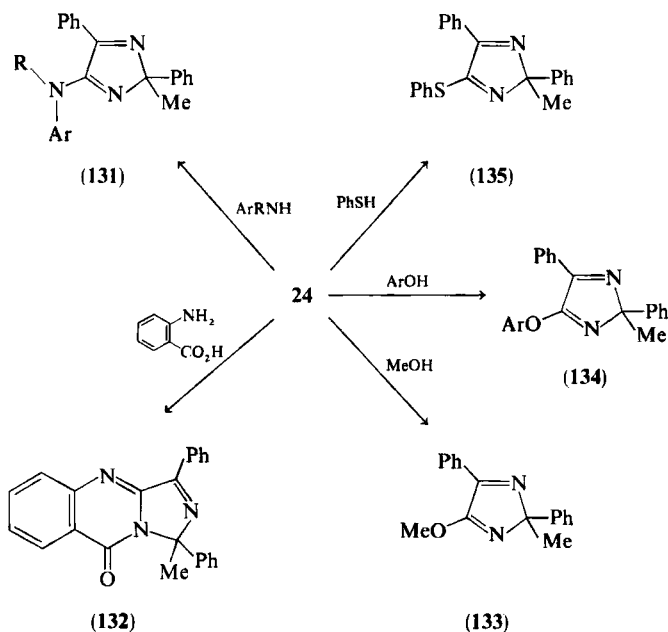
SCHEME 32

2. Grignard Reagents

Methylmagnesium iodide adds to **65**, forming **127** ($\text{R}^1 = \text{R}^2 = \text{Me}$)⁶⁴; with the *N,N'*-dioxide **89** ($n = 2$; $\text{R}^1 = \text{R}^2 = \text{Me}$), the ring-opened oxime **130** is the product.⁷⁴ In the formation of both **129** and **130**, the nucleophile appears to attack consecutively at C-5 and C-2.

3. Displacement of Chlorine

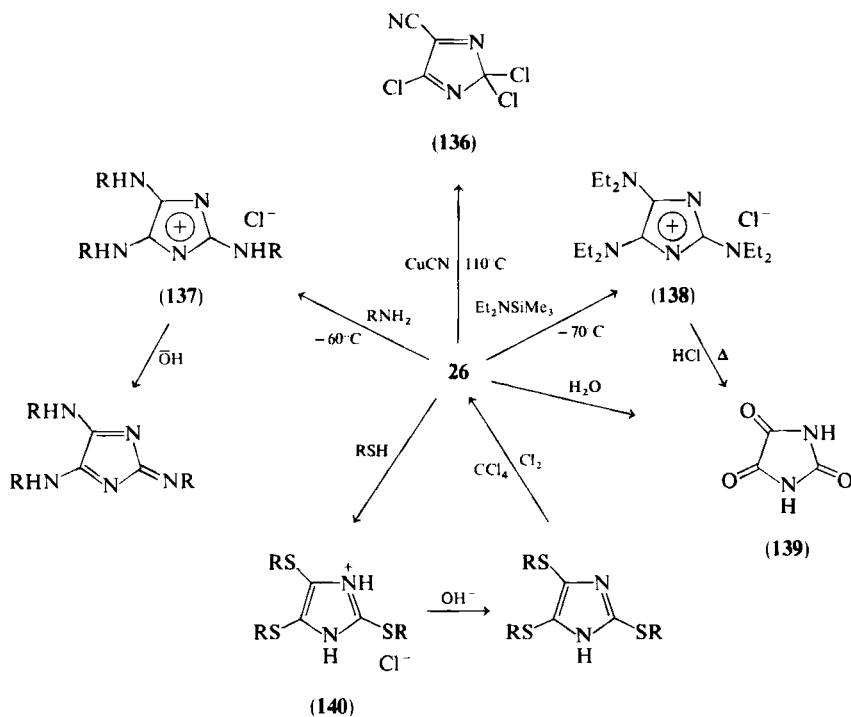
Chlorine is displaced from **24** (Scheme 33) by reaction with primary and secondary aromatic amines to yield **131**,^{32,37} although reaction with 2-



SCHEME 33

aminobenzoic acid gives **132**³⁷; reactions with methanol³² and with phenols^{32,37} yield **133** and **134** respectively; and reaction with thiophenol gives **135**.³⁷ This series of high-yielding reactions complements that of Scheme 8.

Compound **26**, likewise, undergoes a series of displacement reactions (Scheme 34). Whereas reaction with copper(I) cyanide replaces only one chlorine atom to yield **136**,³⁸ all are displaced by reactions with ammonia and isopropylamine,^{38,98} diethyl(trimethylsilyl)amine,⁹⁹ water,³⁸ and thiols³⁸ to give, respectively, **137**–**140**. Some additional transformations are also shown.

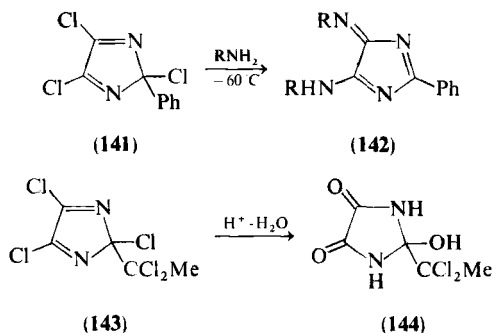


SCHEME 34

The trichloro compound **141** reacts with ammonia, isopropylamine,⁹⁸ or arylamines³⁹ to give **142** (Scheme 35); **143** on hydrolysis is converted to the plant growth regulator **144**.⁴⁰

⁹⁸ K. H. Büchel and H. Erdmann, *Chem. Ber.* **110**, 3226 (1977).

⁹⁹ R. Gompper and K. Bichlmayer, *Angew. Chem., Int. Ed. Engl.* **18**, 156 (1979).

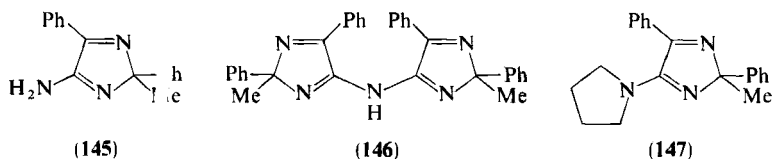


SCHEME 35

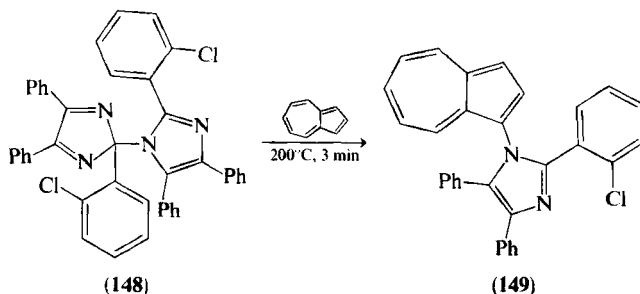
4. Displacement of Other Groups

On treatment with sodium ethoxide in ethanol, dicyano compound **9** is converted to **109**.²¹

At 180°C the hydrochloride salt of **145** is transformed into **146** with excess **145**, whereas with other amines 4-amino derivatives are formed.³⁵ Methanolic hydrogen sulfide yields **12** (R¹ = Ph) from **147**.³⁶



Alkylthio compounds **16** (R¹ = Ph) are oxidized by 30% hydrogen peroxide,²⁷ or by potassium permanganate³² to the corresponding Δ^3 -imidazolin-5-one; sulfonyl chloride transforms disulfide **19** into **24**.³² Alkylthio groups are not displaced by hydrazine.³⁰



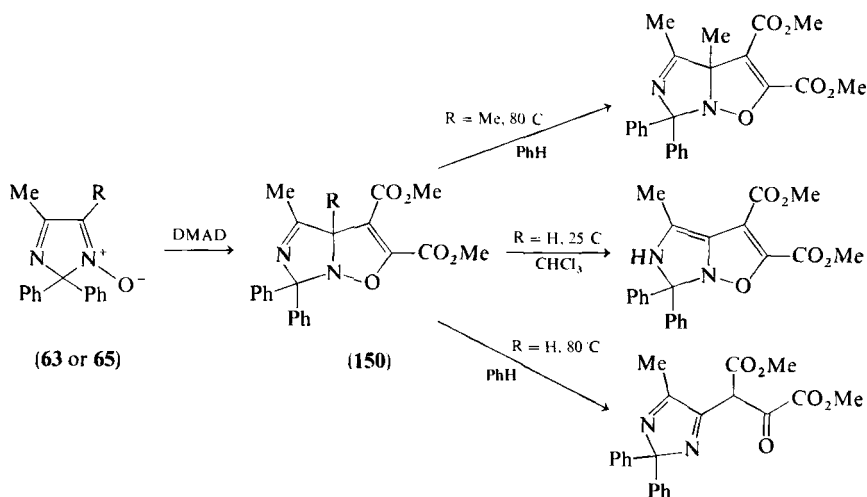
SCHEME 36

In ethanolic hydrochloric acid, **38** (Ar = Ph) is cleaved to a mixture of **111** and **112**.⁵² Thermolysis of **148** in azulene gives **149**, presumably by a radical reaction (Scheme 36).¹⁰⁰

D. REACTIONS WITH CYCLIC TRANSITION STATES

1. Cycloadditions to N-Oxides

N-Oxides **63** and **65**, being nitrones, react with dimethyl acetylenedicarboxylate (DMAD) in a 1,3-dipolar cycloaddition reaction. The initial product **150** may rearrange, depending on the structure of the substrate and the reaction conditions (Scheme 37).⁶⁴

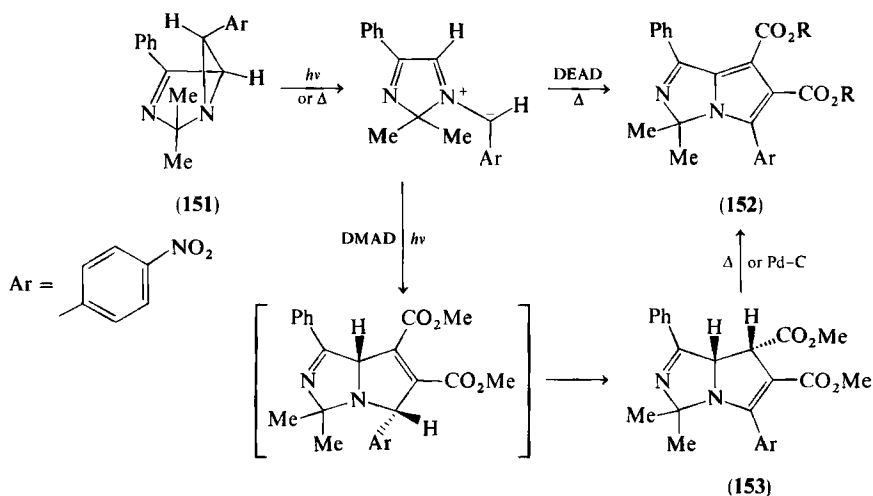


SCHEME 37

2. Cycloadditions to N-Ylides

Thermolysis or photolysis of 1,3-diazabicyclo[3.1.0]hex-3-enes, as in Scheme 22, gives N-ylides that have been trapped by a number of dipolarophiles. Thermolysis of **151** in diethyl acetylenedicarboxylate (DEAD) yielded **152** (R = Et) directly (Scheme 38), presumably via a dihydro intermediate.⁷⁸ Using DMAD, a mixture of **152** (R = Me) and **153** was formed

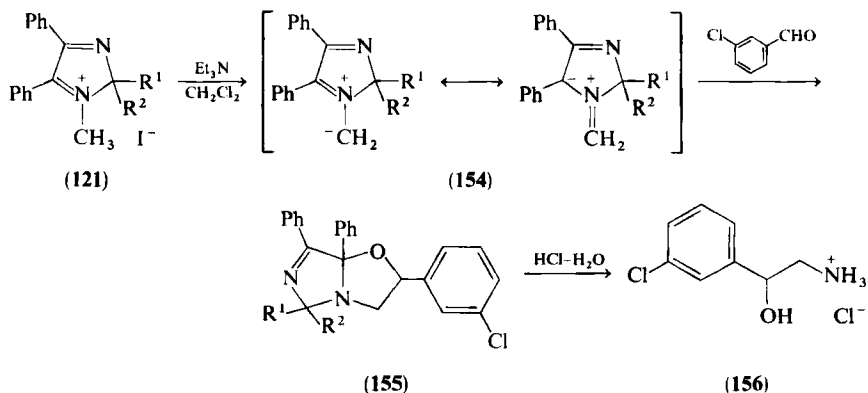
¹⁰⁰ V. I. Erikhov, Y. N. Porshnev, and M. I. Cherkashin, *Khim. Geterotsikl. Soedin.*, 1002 (1976) [*CA* **85**, 159981 (1976)].



SCHEME 38

thermally, whereas irradiation gave **153** (68%), convertible to the corresponding **152** by palladium dehydrogenation.^{76,77} Similar cyclizations have been achieved with diethyl fumarate, diethyl azodicarboxylate, *N*-phenylmaleimide, dibenzoyl ethene (same product from *cis* and *trans* isomers),⁷⁸ and with tetracyanoethene.^{76,77}

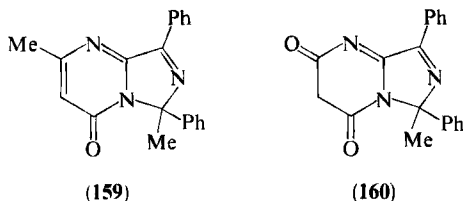
The salts **121** ($R^1 = R^2 = \text{Me}$ or Et) have been shown to add to *m*-chlorobenzaldehyde in the presence of base with the formation of the adducts **155** (Scheme 39).¹¹ It is likely that the *N*-ylide **154** is an intermediate; the *N*-methyl protons were almost completely exchanged after 48 h in acetone- D_2O with triethylamine catalysis. Hydrolysis of **155** yielded the hydroxyamines **156**.¹¹



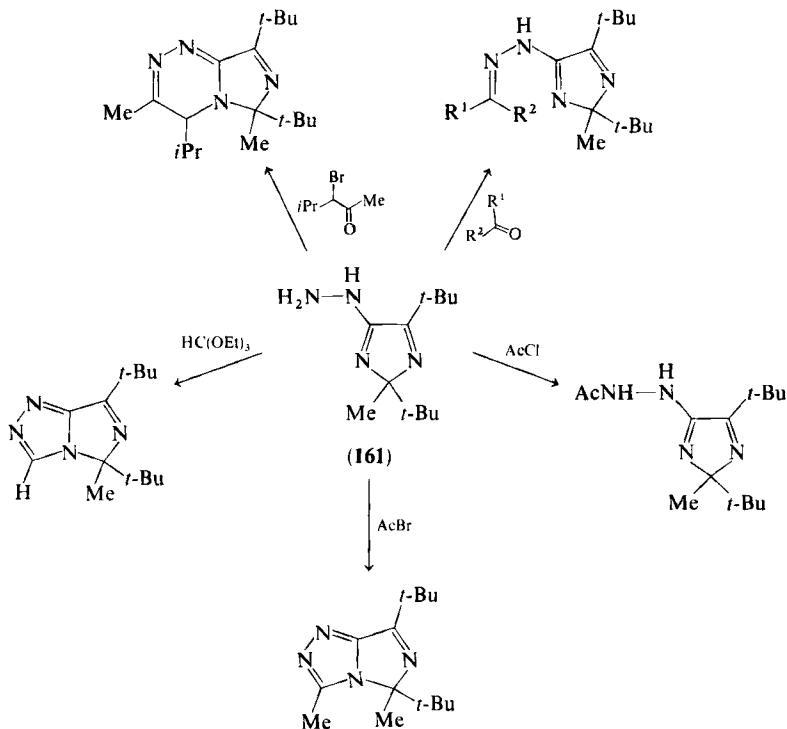
SCHEME 39

2. *N*-Linked

The 4-amino group of **145** is readily monoacylated with acyl or sulfonyl chlorides and isocyanates or isothiocyanates; ethyl acetoacetate and diethyl malonate yield, respectively, **159** and **160**.³⁵ Hydrazides **161** undergo a re-



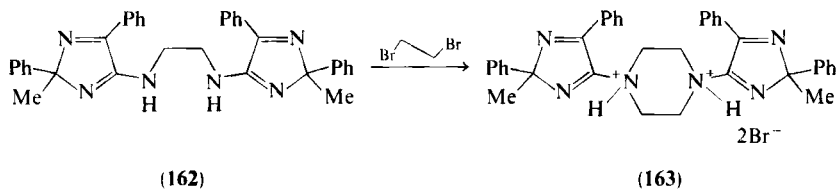
lated series of reactions (Scheme 42).¹⁰¹ The contrast in behavior between acetyl chloride and acetyl bromide is particularly interesting.



SCHEME 42

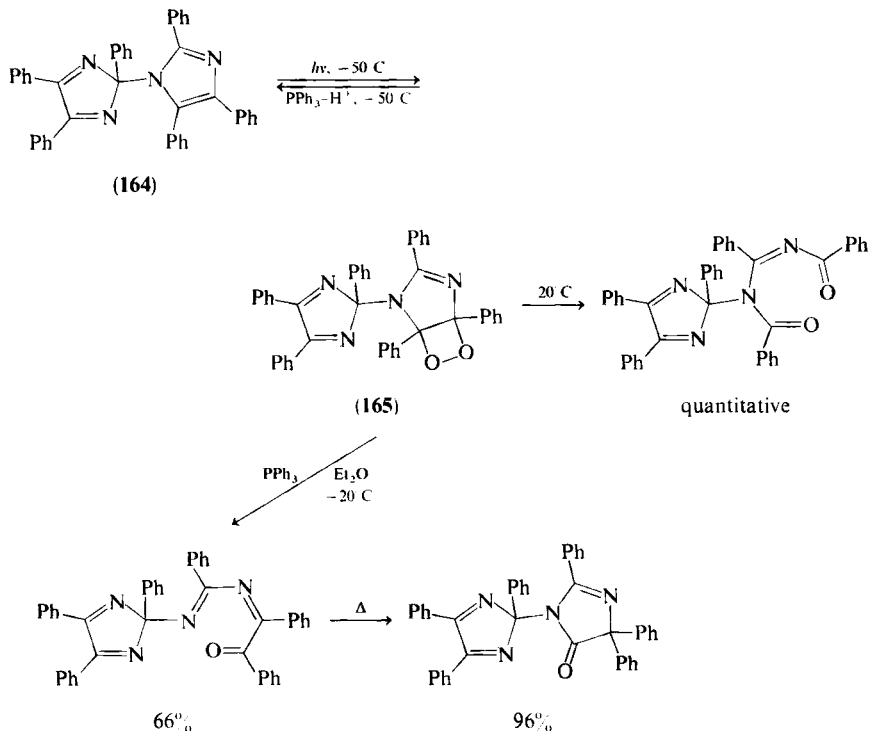
¹⁰¹ F. Asinger, W. Leuchtenberger, and V. Gerber, *Monatsch. Chem.* **105**, 38 (1974).

With 1,2-dibromoethane, **162** gives a small amount of the salt **163** (Scheme 43).³⁷



SCHEME 43

The methylene-blue sensitized photooxygenation of **164** yields the isolable dioxetane **165** (70%), the first of its kind to be isolated from an imidazole, presumably via the sequence of Schemes 10 and 26. Some of its reactions are illustrated (Scheme 44).⁸⁶



SCHEME 44

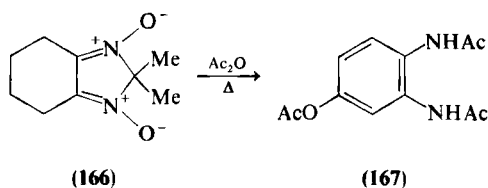
3. *O*-Linked

Hydroperoxy compounds **29** and **30** are reduced in high yields to their hydroxy analogs by triphenylphosphine.^{44,45}

The deoxygenation of *N*-oxides was discussed earlier (Section II,D,3).

Acid hydrolysis of **85** to yield equimolar amounts of **86** and **87** (Scheme 20)⁷¹ probably proceeds via initial protonation to give **84**.

The conversion of **166** to **167** (Scheme 45)⁷⁴ most likely involves initial acylation of an *N*-oxide function. Interestingly, **63** (but perhaps the authors meant **65**) did not show typical *N*-oxide reactions either with phosphorus oxychloride or with acetic anhydride.⁶⁴



SCHEME 45

The 4*H*-Imidazoles

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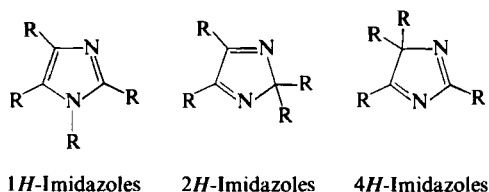
*Department of Chemistry, University of Florida,
Gainesville, Florida*

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I. Introduction

The 4*H*-imidazoles, like their 2*H* counterparts described in the previous chapter,¹ have a tetrahedral carbon atom in the ring and thus, unlike the familiar 1*H*-imidazoles (Scheme 1), are nonaromatic. The 2*H* and 4*H* isomers also differ from each other structurally in the relative arrangements of the two C=N bonds; however, this does not result in so marked a difference in chemical properties, as is found between the 3*H*- and 4*H*-pyrazoles.²



SCHEME 1

¹ M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **35**, 375 (1983).

² M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **34**, 1, 53 (1983).

The 4*H*-imidazoles have not previously been reviewed comprehensively. In earlier reviews on the 1*H* compounds³⁻⁵ isolated examples are discussed, although in a later work a more thorough treatment has been given.⁶ An attempt has been made in the present article to include all known 4*H*-imidazoles: using a CAS "on line" substructure computer search, *Chemical Abstracts* have been covered up to and including Issue 4 of Volume 97, and a few additional references have been included directly from the more common international journals. Structures having exocyclic double bonds have been excluded; benz-fused systems cannot be drawn in this series.

II. Synthesis of 4*H*-Imidazoles

One interesting difference between the known examples of 2*H*- and 4*H*-imidazoles is that nearly all in the latter group contain at least one hetero-linked substituent. This arises because the major synthetic approach is via imidazolone derivatives (see next section); a second important route using 1,2-diketones places an OH group at C-4, and electrophilic additions to 1*H*-imidazoles also tend to introduce heteroatoms at this site.

A. BY TRANSFORMATION OF IMIDAZOLONE DERIVATIVES

Electrophilic attack of the HN—C=X moiety in imidazolone derivatives at X (which has usually been sulfur) can result in 4*H*-imidazoles. This has been the most commonly used method for the preparation of these compounds.

1. 5,5-Disubstituted Imidazolidine-2,4-dithiones (Dithiohydantoins)

a. *Alkylation.* Reaction of dithiohydantoins **1** with excess of an alkyl halide, sulfate, or aryl sulfonate, in the presence of base, yields the dialkyl derivatives **2** (Scheme 2). Most frequently, R¹R² has been Ph₂,⁷⁻⁹ Me₂,^{9,10}

³ K. Hofmann, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Part 1, p. 363 Wiley (Interscience), New York, 1953.

⁴ A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Russ. Chem. Rev. (Engl. Transl.)* **35**, 122 (1966).

⁵ M. R. Grimmett, *Adv. Heterocycl. Chem.* **12**, 103 (1970); **27**, 241 (1980).

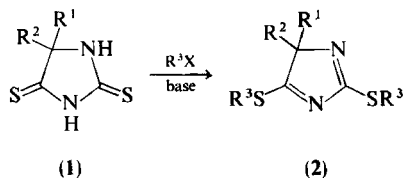
⁶ M. R. Grimmett, in "Comprehensive Heterocyclic Chemistry" (A. R. Katritzky and C. W. Rees, eds.), Vol. 4, Chapters 4.6-4.8. Pergamon, Oxford, 1984.

⁷ H. C. Carrington and W. S. Waring, *J. Chem. Soc.*, 354 (1950).

⁸ K. Lempert, J. Nyitrai, and P. Sohar, *Tetrahedron Lett.*, 1975 (1965).

⁹ J. D. Kendall and G. F. Duffin, U.S. Patent 2,704,755 (1955) [*CA* **49**, 10107 (1955)]; British Patent 734,792 (1955) [*CA* **50**, 1502 (1956)].

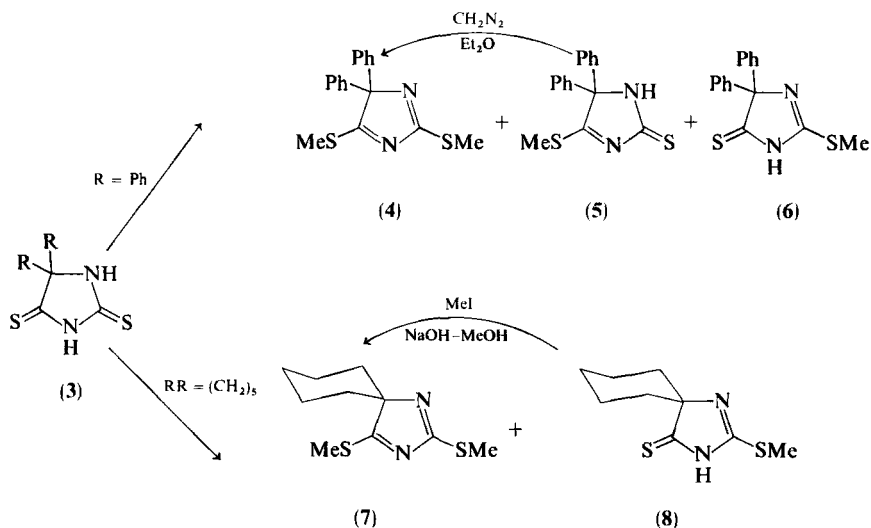
¹⁰ R. Hazard, J. Cheymol, P. Chabrier, and K. Smarzewska, *Bull. Soc. Chim. Fr.*, 228 (1949).



SCHEME 2

and $(\text{CH}_2)_5$,^{7,9} but also Et_2 ,⁹ $(\text{CH}_2)_4$,⁹ $(\text{PhCH}_2)_2$,¹¹ and in one case the two substituents have been different (Me and PhCH_2).⁹ In nearly all examples, R^3 has been Me,^{7,9-11} the exception being Et.⁹

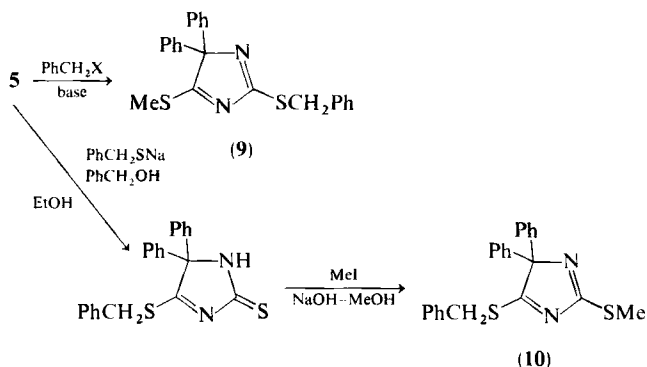
The reaction proceeds in two stages,¹⁰ and the products depend⁷ both on the conditions and on the nature of R^1 and R^2 . Thus **3** ($\text{R} = \text{Ph}$) gives **4** (88%) on reaction with excess methyl iodide in the presence of methanolic sodium hydrogen carbonate, and a mixture of **4** (32%) and **5** (15%) is formed in ethanolic sodium hydroxide. Compounds **4** (25%), **5** (19%), and **6** (13%) are produced on reaction of **3** with dimethyl sulfate in aqueous sodium hydroxide (Scheme 3).⁷ For **3** [$\text{RR} = (\text{CH}_2)_5$], methyl iodide fails to give **7**, but dimethyl sulfate in aqueous sodium hydroxide yields a mixture of **7** (33%), **8** (30%), and a small amount of N-methylated products.⁷ Conversions of **5** to **4** (40%) and **8** to **7** (84%) have also been achieved⁷ (Scheme 3).



SCHEME 3

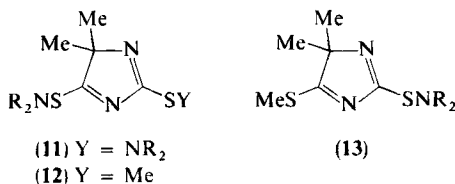
¹¹ R. Markovits-Kornis, J. Nyitrai, and K. Lempert, *Chem. Ber.* **104**, 3080 (1971).

Isomeric compounds **9** and **10**, in which the two S-substituents are different, have been prepared by the sequence of Scheme 4.^{8,12}



In methoxybenzene at 153°C, both **5** and **6** disproportionated to **4** (8–13%), **3**, and several other products; **8** likewise gave 17% each of **7** and the corresponding **3**.¹³

b. Oxidative Amination. With iodine and a secondary aliphatic amine in ether, the sulfenamides **11**–**13** were prepared from the appropriate dithiohydantoin or *S*-methyl derivatives.¹⁴ Compounds **11** were claimed to show antithyroid activity.¹⁵



2. 1,3-Dichloro-5,5-dimethylimidazolidine-2,4-dione

The bissulfonium salts **15**, formed from **14** and thioethers, undergo a Stevens rearrangement with the highly selective formation of two (**16** and **17**)

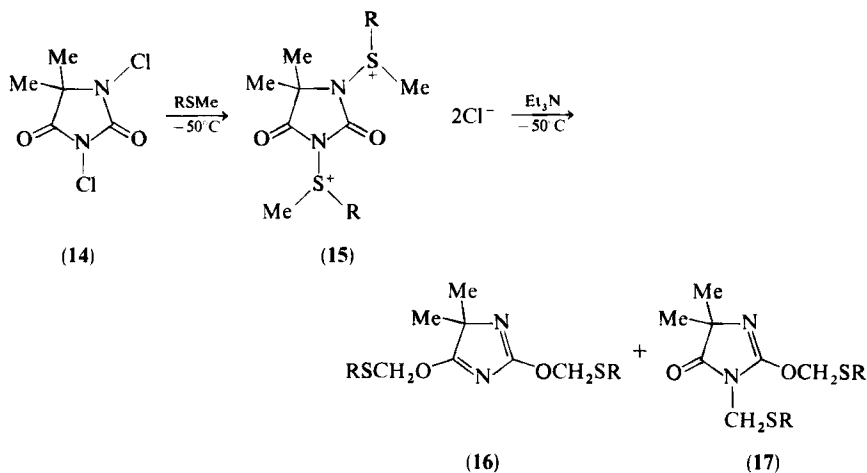
¹² K. Lempert and J. Nyitrai, *Tetrahedron Lett.*, 2927 (1965); *Acta Chim. Acad. Sci. Hung.* **41**, 95 (1967) [*CA* **67**, 21867 (1967)].

¹³ J. Fetter, J. Nyitrai, and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **79**, 197 (1973) [*CA* **80**, 26594 (1974)].

¹⁴ P. Chabrier and K. Smarzewska, *C. R. Hebd. Seances Acad. Sci., Ser. C.* **230**, 656 (1950); P. Chabrier, S.-H. Renard, and K. Smarzewska, *Bull. Soc. Chim. Fr.*, 1167 (1950).

¹⁵ J. Cheymol, P. Chabrier, and Y. Gay, *Arch. Int. Pharmacodyn. Ther.* **90**, 78 (1952) [*CA* **46**, 10409 (1952)].

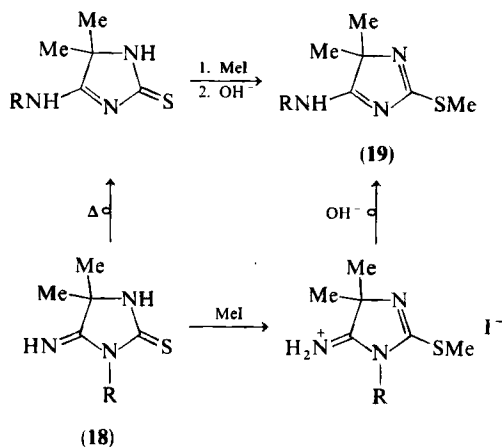
out of five possible products (Scheme 5).¹⁶ For most alkyl R, a mixture of roughly equal amounts of both isomers were formed (30–48%); for R = Me or Ph, isomer **16** predominated strongly.



SCHEME 5

3. 4-Imino-5,5-dimethylimidazolidine-2-thiones

Iminothiones **18** have been transformed into the 4*H*-imidazoles **19** by two different routes, both involving Dimroth rearrangements (Scheme 6).¹⁷



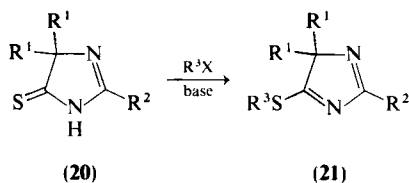
SCHEME 6

¹⁶ E. Vilsmaier, R. Bayer, U. Welz, and K.-H. Dittrich, *Chem. Ber.* **111**, 1147 (1978).

¹⁷ A. F. McKay, C. Podesva, and M. E. Kreling, *J. Org. Chem.* **27**, 2884 (1962).

4. 4,4-Disubstituted 2-Imidazoline-5-thiones

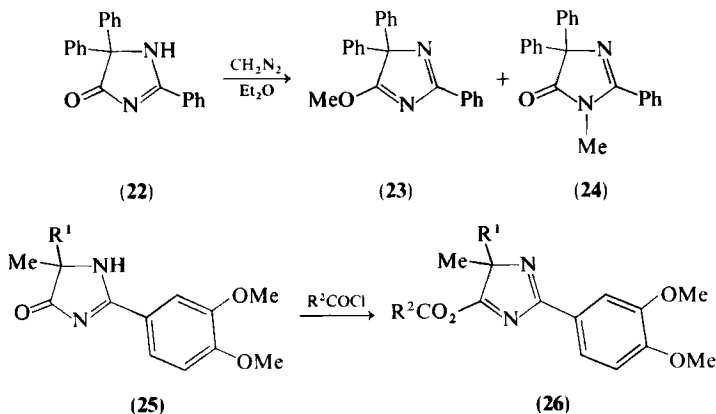
Monoalkylation of compounds **20** (Scheme 7), using an alkyl halide and base, appears to occur exclusively at sulfur, yielding **21**.¹⁸⁻²⁰ R^1R^1 has been Ph_2 ,^{19,20} Me_2 ,¹⁸ or $(\text{CH}_2)_5$ ¹⁸; R^2 has been Me ,^{18,19} PhCH_2 ,¹⁸ or Ph .^{19,20}, and R^3 has been Me ,¹⁸⁻²⁰ Et ,¹⁸ or PhCH_2 .¹⁹



SCHEME 7

5. 4,4-Disubstituted 2-Imidazolin-5-ones

Alkylation of imidazolinones, in the presence of base, generally occurs at ring nitrogen rather than at the carbonyl oxygen. Reaction with diazomethane, however, gives a mixture of **23** (28%) and **24** (26%) from **22** (Scheme 8).¹⁹ Structures **25** are claimed to be acylated on oxygen to yield **26** by using acyl chlorides but on nitrogen by using acyl anhydrides.²¹



SCHEME 8

¹⁸ J. D. Kendall and G. F. Duffin, British Patent 749,141 (1956) [CA 51, 1289 (1957)].

¹⁹ J. Nyitrai and K. Lempert, *Tetrahedron* **25**, 4265 (1969).

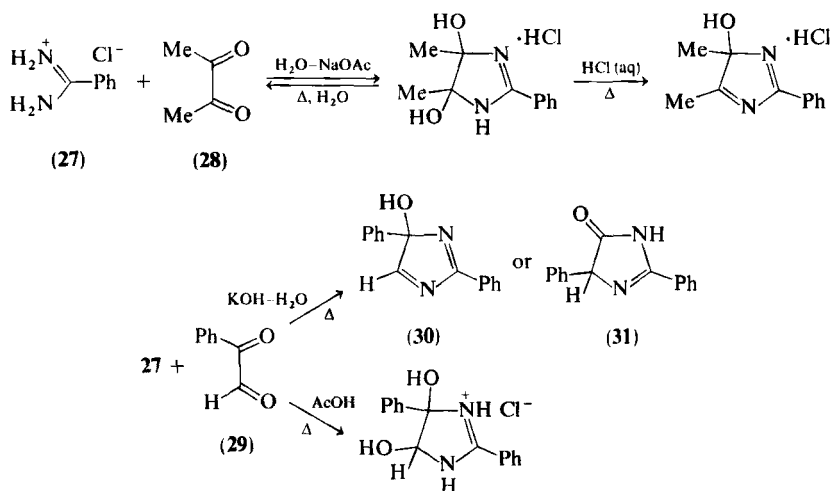
²⁰ J. Nyitrai and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **73**, 43 (1972) [CA 77, 164600 (1972)].

²¹ Y. Y. Usaevich, I. K. Fel'dman, and E. I. Boksiner, *Khim. Geterotsikl. Soedin.*, 746 (1971) [CA 76, 24446 (1972)].

B. FROM KETONES AND AMIDINES

1. α -Diketones

Early claims to have prepared 4-hydroxy-4*H*-imidazoles from benzamidine hydrochloride (**27**) and 2,3-butanedione (**28**),²² or phenylethane-1,2-dione (**29**),²³ appear to be substantially correct (Scheme 9). Although this work has not been repeated, analogous intermediates have been observed subsequently in related reactions. Waugh and co-workers²³ recognized that **30** might well have been the rearranged isomer **31**. (see Section IV,A,1,b).



SCHEME 9

During an investigation into the mechanism of the Voges–Proskauer reaction (a color-forming process²⁴ resulting from base-catalyzed interaction between **28** and guanidine derivatives²⁵), two independent groups^{26,27} found that a 4-hydroxy-4*H*-imidazole was an intermediate. Thus, in neutral conditions, 1-phenyl-1,2-propanedione (**32**) reacted with guanidines **33**, forming isolable **34**, which subsequently with base gave colored products (Scheme 10).

²² O. Diels and K. Schleich, *Ber. Dtsch. Chem. Ges.* **49**, 1711 (1916).

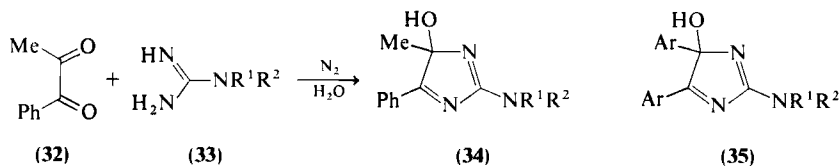
²³ R. C. Waugh, J. B. Ekeley, and A. R. Ronzio, *J. Am. Chem. Soc.* **64**, 2028 (1942).

²⁴ O. Voges and B. Proskauer, *Z. Hyg. Infektionskr.* **28**, 20 (1898).

²⁵ A. Harden and D. Norris, *J. Physiol. (London)* **42**, 332 (1911) [*CA* **5**, 3465 (1911)]; P. Eggleston, S. R. Elsdon, and N. Gough, *Biochem. J.* **37**, 526 (1943), and references cited therein.

²⁶ T. Nishimura, H. Toki, T. Ueno, S. Shibamoto, and T. Imai, *Chem. Lett.*, 649 (1972).

²⁷ K. Kijima and T. Sakaguchi, *Yakugaku Zasshi* **93**, 831 (1973) [*CA* **80**, 2818 (1974)].

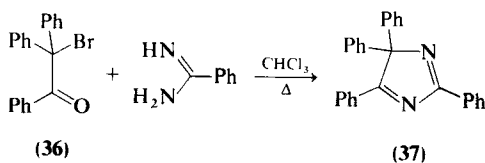


SCHEME 10

The reaction works well when R^1 and R^2 are alkyl or benzyl, or when NR^1R^2 is a cyclic secondary amine.²⁸⁻³⁰ It also works with benzil and its para-substituted derivatives and with guanidine and its mono-substituted derivatives, giving high yields of products **35** having Ar = phenyl para-substituted with H, Cl, Me, and MeO,³¹⁻³³ and $R^1 = R^2 = H$,^{31,32} $R^1 = H$, and $R^2 =$ alkyl or benzyl.^{33,34} The highest yields are obtained in methanol at room temperature.³¹

2. α -Bromoketones

Only one example has been reported of the potentially quite general approach of using α -bromoketones to prepare 4H-imidazoles. Reaction between a 3.5-mol excess of benzamidine and **36** (Scheme 11) gave the tetraphenyl derivative **37** (18%).³⁵



SCHEME 11

²⁸ T. Nishimura and H. Toku, Jpn. Kokai 74/48,663 (1974) [CA **82**, 16842 (1975)].

²⁹ T. Nishimura, K. Nakano, S. Shibamoto, and K. Kitajima, *J. Heterocycl. Chem.* **12**, 471 (1975).

³⁰ T. Sakaguchi and S. Tanabe, *Yakugaku Zasshi* **97**, 223 (1977) [CA **87**, 38405 (1977)].

³¹ T. Nishimura and K. Kitajima, *J. Org. Chem.* **44**, 818 (1979).

³² T. Nishimura, K. Kitajima, and Y. Kazuno, Jpn. Kokai 79/48,762 (1979) [CA **91**, 175348 (1979)]; *ibid.* 79/48,763 (1979) [CA **91**, 175349 (1979)].

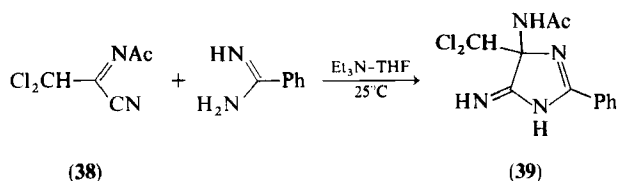
³³ T. Nishimura, Jpn. Kokai 80/72,173 (1980) [CA **94**, 65680 (1981)].

³⁴ T. Nishimura, K. Kitajima, S. Kurozumi, K. Komoriya, and Y. Hashimoto, Jpn. Kokai 79/112,864 (1979) [CA **92**, 41957 (1980)].

³⁵ D. M. White and J. Sonnenberg, *J. Org. Chem.* **29**, 1926 (1964).

C. FROM IMINES AND AMIDINES

Structures **39** are formed (51–93%) from benzamidine and the iminonitriles **38** (Scheme 12).³⁶

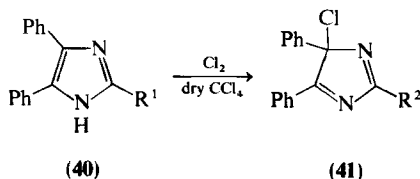


SCHEME 12

D. BY REACTION BETWEEN 1H-IMIDAZOLES AND ELECTROPHILES

1. Chlorine

Imidazoles unsubstituted at the 4- and 5-positions give polychloro-2H-imidazoles with chlorine.¹ In contrast, the 4,5-diphenyl compounds **40** (R¹ = H, Me, Ph) yield 4H-imidazoles **41**, in which R² = Cl, CCl₃, and Ph, respectively (Scheme 13).^{37,38}



SCHEME 13

2. Oxygen

The base-catalyzed chemiluminescence of triphenylimidazole (**42**, lophine) in the presence of oxygen, first reported by Radziszewski,³⁹ was later shown

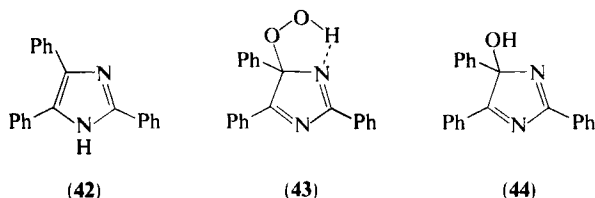
³⁶ T. K. Vinogradova, G. N. Mis'kevich, and B. S. Drach, *Zh. Org. Khim.* **16**, 1869 (1981) [*CA* **94**, 84010 (1981)].

³⁷ K. H. Büchel and H. Erdmann, *Chem. Ber.* **109**, 1638 (1976).

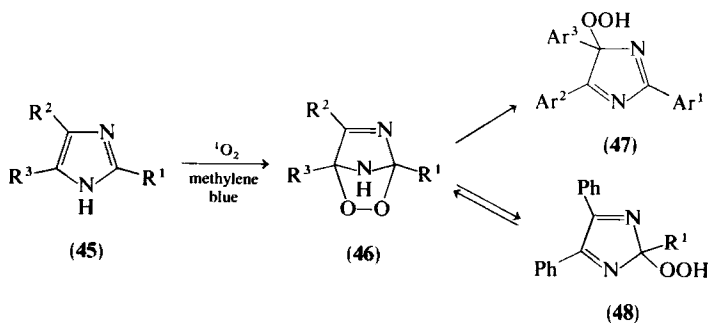
³⁸ K. H. Büchel, Ger. Offen. 2,441,820 (1976) [*CA* **84**, 180223 (1976)].

³⁹ R. Radziszewski, *Ber. Dtsch. Chem. Ges.* **10**, 70 (1877).

to result from rearrangement of the 4-hydroperoxide **43**^{40,41} (Section IV,A,1,c). The 4-hydroxy compound **44** had also been identified in the reaction mixture.⁴² Structure **43**⁴⁰⁻⁴⁴ and a number of substituted phenyl analogs^{41,44} may be prepared in good yields by the methylene-blue sensitized photooxygenation of **42** and its derivatives, a reaction analogous to that shown by 2,3,4,5-tetraphenylpyrrole.⁴³



The mechanism of photooxygenation has been studied for a range of substituted imidazoles **45** (Scheme 14).⁴⁵ It proceeds via the endoperoxide **46**, which has been detected by ¹H-NMR spectroscopy in certain instances,⁴⁶ giving **47** for triarylimidazoles, **48** reversibly at low temperatures for R¹ = alkyl, R² = R³ = Ph,^{1,47,48} and a variety of different products for other substituents.⁴⁵



SCHEME 14

⁴⁰ J. Sonnenberg and D. M. White, *J. Am. Chem. Soc.* **86**, 5685 (1964).

⁴¹ E. H. White and M. J. C. Harding, *J. Am. Chem. Soc.* **86**, 5686 (1964).

⁴² C. Dufraisse, G. Rio, and A. Ranjon, *C. R. Hebd. Seances Acad. Sci., Ser. C* **246**, 1337 (1958).

⁴³ C. Dufraisse, G. Rio, A. Ranjon, and O. Pouchot, *C. R. Hebd. Seances Acad. Sci., Ser. C* **261**, 3133 (1965).

⁴⁴ K. Maeda and T. Hayashi, *Bull. Chem. Soc. Jpn.* **44**, 533 (1971).

⁴⁵ W. Wasserman, M. S. Wolff, K. Stiller, I. Saito, and J. E. Pickett, *Tetrahedron* **37**, Suppl. 1, 191 (1981).

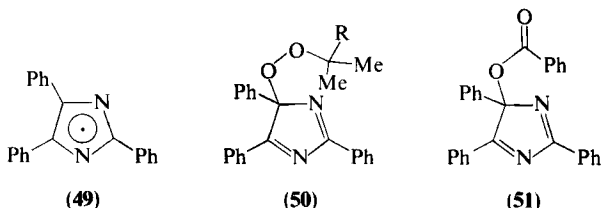
⁴⁶ H.-S. Ryang and C. S. Foote, *J. Am. Chem. Soc.* **101**, 6683 (1979).

⁴⁷ M. L. Graziano, M. R. Iesce, and R. Scarpati, *J. C. S. Chem. Commun.*, 7 (1979).

⁴⁸ M. L. Graziano, G. Curato, and R. Scarpati, *J. Heterocycl. Chem.* **16**, 1571 (1979).

3. Peroxides

Addition of hydrogen peroxide to the triphenylimidazolyl (lophyl) radical (49), generated from its piezochromic dimer, yields 43; tertiary hydroperoxides likewise give 50 (R = Me, Ph).⁴⁰



Dibenzoyl peroxide adds to 42 in benzene, again via 49, forming 51. The reaction also works with other imidazoles having at least one aryl and up to two alkyl substituents.⁴⁹

4. Hexacyanoferrate(III)

The oxidation of 42 and its aryl-substituted analogs to give dimers containing 1*H*-, 2*H*-, and 4*H*-imidazole residues⁵⁰⁻⁵⁴ was discussed in the previous review.¹ Opinions differ as to the structures of certain of the products, although that from hexacyanoferrate(III) oxidation in benzene is the 1,2'-isomer.⁵⁵

Hexacyanoferrate(III) oxidation of 52 in dioxane yields 53, which undergoes base-catalyzed addition of ethanol, forming 54 (Scheme 15). Oxidation in the presence of ethanol gives a mixture of 54, 55, and 56, the ratio depending on the presence or absence of oxygen.⁵⁶ The structure of 56 was deduced spectroscopically and by independent synthesis from 54.

⁴⁹ H. Lettau and H. J. Heckel, *Z. Chem.* **11**, 62 (1971) [*CA* **74**, 125561 (1971)].

⁵⁰ D. M. White and J. Sonnenberg, *J. Am. Chem. Soc.* **88**, 3825 (1966).

⁵¹ H. Tanino, T. Kondo, K. Okada, and T. Goto, *Bull. Chem. Soc. Jpn.* **45**, 1474 (1972).

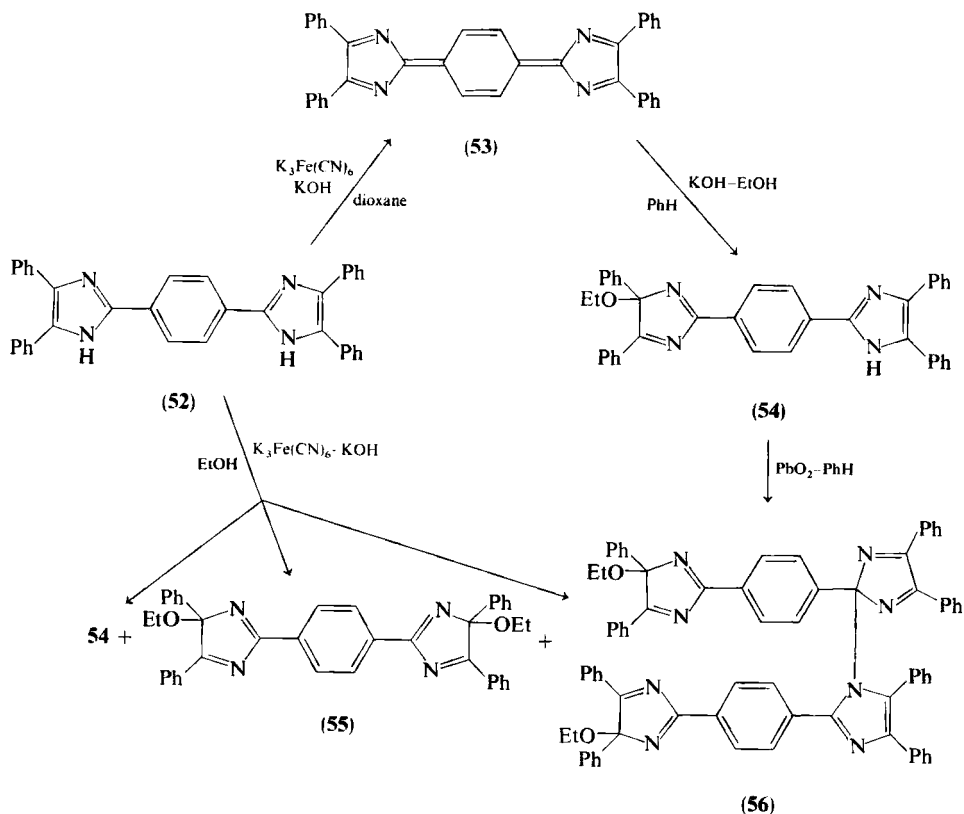
⁵² M. Libert and C. Caillet, *Bull. Soc. Chim. Fr.* 345 (1976).

⁵³ U. Lang and H. Baumgärtel, *J. Electroanal. Chem. Interfacial Electrochem.* **78**, 133 (1977) [*CA* **87**, 208569 (1977)].

⁵⁴ T. Goto, H. Tanino, and T. Kondo, *Chem. Lett.*, 431 (1980).

⁵⁵ L. A. Cescon, G. R. Caraor, R. Dessauer, E. F. Silversmith, and E. J. Urban, *J. Org. Chem.* **36**, 2262 (1971).

⁵⁶ Y. Sakaino, H. Kakisawa, T. Kusumi, and K. Maeda, *J. Org. Chem.* **44**, 1241 (1979).



SCHEME 15

E. FROM AZIRINES

1. 3-Dimethylaminoazirines with Cyclic Amides

5-Dimethylamino-4H-imidazoles are common products from reactions of 3-dimethylaminoazirines with cyclic amides, although the mechanism depends heavily on the structure of the cyclic amide and on the conditions.⁵⁷⁻⁶⁰

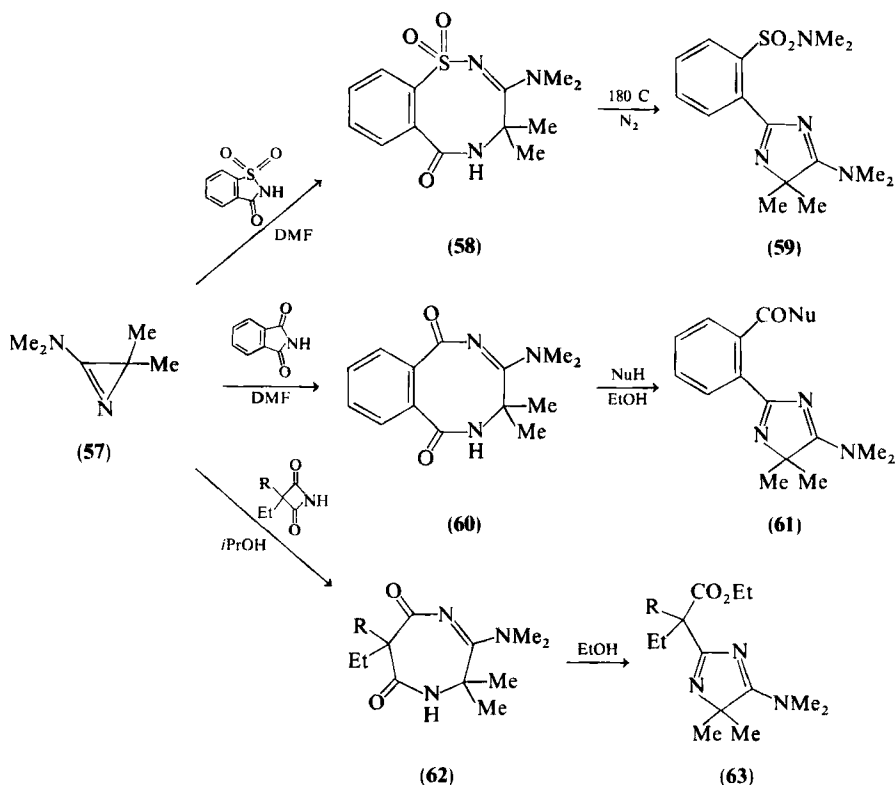
⁵⁷ S. Chaloupka, P. Vittorelli, H. Heimgartner, H. Schmid, H. Link, K. Bernauer, and W. E. Oberhansli, *Helv. Chim. Acta* **60**, 2476 (1977).

⁵⁸ B. Scholl, J. H. Bieri, and H. Heimgartner, *Helv. Chim. Acta* **61**, 3050 (1978).

⁵⁹ G. Mukherjee-Müller, S. Chaloupka, H. Heimgartner, H. Schmid, H. Link, K. Bernauer, P. Schönholzer, and J. J. Daly, *Helv. Chim. Acta* **62**, 768 (1979).

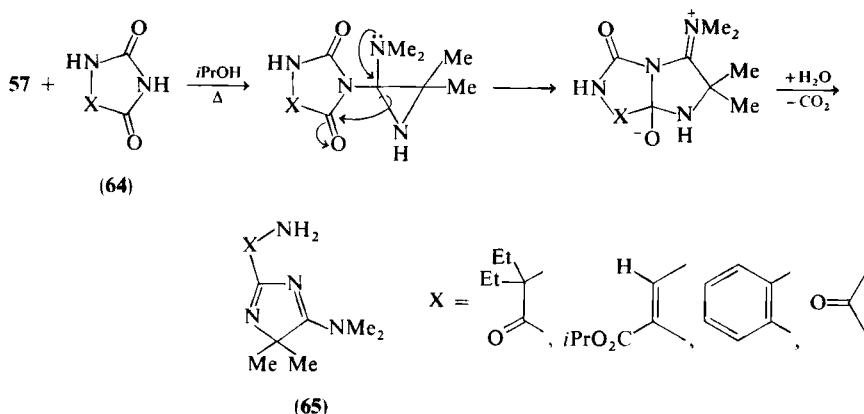
⁶⁰ H. Link, K. Bernauer, J. J. Daly, S. Chaloupka, and H. Heimgartner, *Helv. Chim. Acta* **64**, 49 (1981).

With five- (or four)-membered-ring cyclic imides (Scheme 16) **57** initially gives isolable eight- (or seven)-membered ring intermediates (**58**, **60**, and **62**), which can be converted readily to products **59**, **61**,⁵⁷ and **63**.⁵⁸ The key step appears to be transannular attack of the imine nitrogen of the intermediate on the amide carbonyl. This is followed by attack of a nucleophile and ring opening via a number of possible pathways.^{57,58}



SCHEME 16

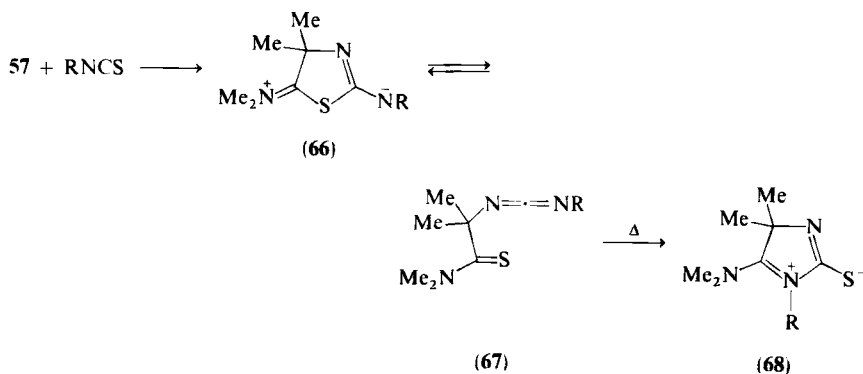
For cyclic amides containing the NHCONHCO moiety (**64**, Scheme 17), the reaction follows a different course, not involving a medium-ring intermediate, and losing carbon dioxide to give products **65**.⁵⁹ When $\text{X} = \text{COCH}_2$, yet another mechanism is observed and no 4H-imidazole is formed.⁶⁰



SCHEME 17

2. 3-Dialkylaminoazirines with Heterocumulenenes

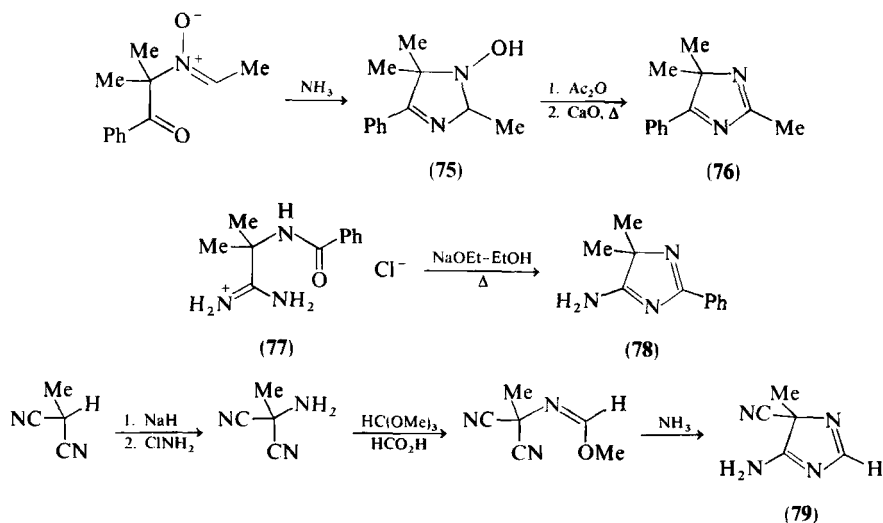
With isothiocyanates, **57** generally yields the isothiazolium betaines **66** (Scheme 18).⁶¹ However, when R is bulky an equilibrium exists with the carbodiimide **67**, which gives the imidazolium betaine **68** on heating⁶² for R = *i*Pr or spontaneously⁶¹ for R = Ph. Alternative mechanisms have been discussed.



SCHEME 18

⁶¹ U. Schmid, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **62**, 160 (1979), and references cited therein.

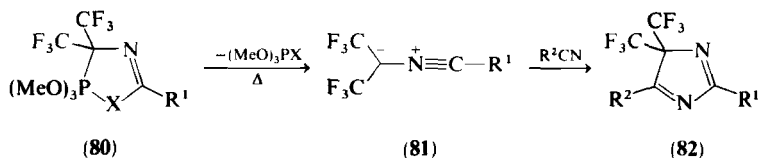
⁶² E. Schaumann, H. Behr, and G. Adiwidjaja, *Liebigs Ann. Chem.*, 1322 (1979).



SCHEME 20

2. By 1,3-Dipolar Cycloaddition

Thermolysis of the azaphospholines **80** ($X = O^{68}$ or S^{69}) generates the *N*-ylides **81** (Scheme 21), which add to nitriles regiospecifically to give high yields of **82** ($R^2 = Ph$ or CO_2Et).



SCHEME 21

3. From 2H-Imidazoles

On prolonged standing in acid solution, **83** is converted to **84** (Scheme 22).⁵¹ Salt **86**, prepared readily from **85**,⁷⁰ can give 4*H*-imidazoles, including **87**⁷¹ and **88**,⁷² on addition of nucleophiles.

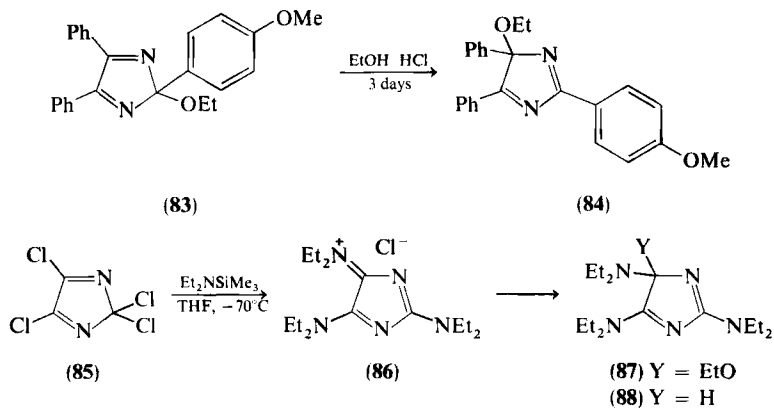
⁶⁸ K. Burger and K. Einhellig, *Chem. Ber.* **106**, 3421 (1973).

⁶⁹ K. Burger and R. Ottlinger, *J. Fluorine Chem.* **12**, 519 (1978).

⁷⁰ R. Gompper and K.-P. Bichlmayer, *Angew. Chem., Int. Ed. Engl.* **18**, 156 (1979).

⁷¹ R. Gompper and K.-P. Bichlmayer, *Tetrahedron Lett.* **21**, 2879 (1980).

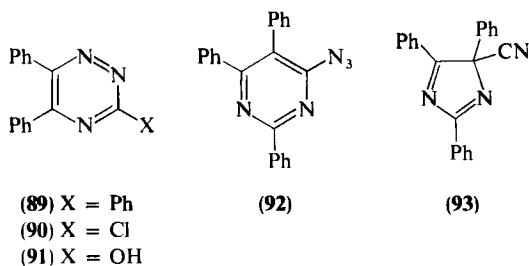
⁷² R. Gompper, M. Junius, and H.-U. Wagner, *Tetrahedron Lett.* **22**, 2973 (1981).



SCHEME 22

4. From Azines

Treatment of **89**, **90**,⁷³ or **91**⁷⁴ with phenylmagnesium bromide gives **37** as one of the products. Thermolysis of **92** gives **93**⁷⁵; a 2-azidopyrimidine gave instead a 3*H*-pyrazole.⁷⁶



G. METHODS FOR *N*-OXIDES

Oxidation (PbO_2) of **75** yields **94** directly⁶⁵; both its isomer **95**, and the *N,N'*-dioxide **96** have been prepared from an *N*-hydroxyimidazoline *N'*-

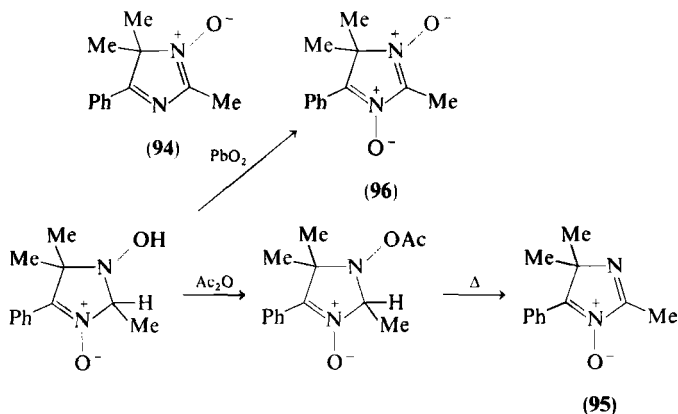
⁷³ A. Mustafa, A. K. Mansour, and H. A. A. Zaher, *J. Prakt. Chem.* **313**, 699 (1971).

⁷⁴ J. Daunis and C. Pigière, *Bull. Soc. Chim. Fr.*, 2818 (1973).

⁷⁵ L. Giammanco and F. P. Invidiata, *Atti Accad. Sci., Lett. Arti Palermo, Parte 1* **31**, 225 (1972) [*CA* **79**, 105177 (1973)].

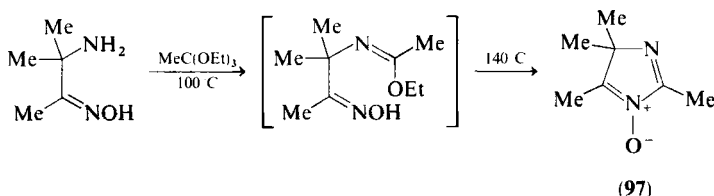
⁷⁶ C. Wentrup and W. D. Crow, *Tetrahedron* **27**, 361 (1971).

oxide as shown (Scheme 23).^{65,77,78} Analogs of **95** have also been prepared with other substituents.⁷⁷



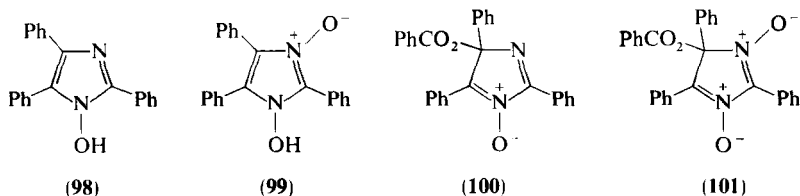
SCHEME 23

The *N*-oxide **97**, prepared as in Scheme 24, is somewhat unstable, being best stored as its hydrochloride.⁷⁹



SCHEME 24

Addition of dibenzoyl peroxide to **98** and **99** yields, respectively, **100** and **101**,⁴⁹ by a radical process.



⁷⁷ L. B. Volodarskii, V. S. Kobrin, and Y. G. Putsykin, *Khim. Geterotsikl. Soedin.*, 1241 (1972) [*CA* **78**, 4188 (1973)].

⁷⁸ S. A. Amitina and L. B. Volodarskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2135 (1976) [*CA* **86**, 106467 (1977)].

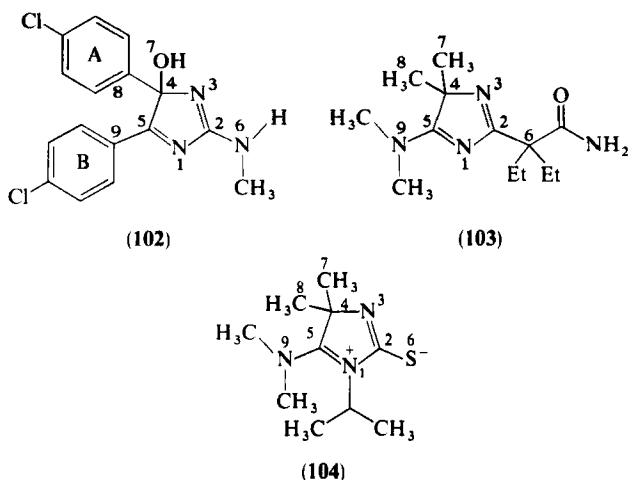
⁷⁹ H. Gnichtel, W. Griebenow, and W. Löwe, *Chem. Ber.* **105**, 1865 (1972).

III. Structure and Physical Properties

A. STRUCTURE

1. X-Ray Crystallography

Data have been published for two free bases (**102**⁸⁰ and **103**⁵⁹) and one betaine (**104**).⁶² Bond distances and angles (numbered as in the structures) are given in Table I.



In Structure **102**, ring A is rotated by 96.2° out of the plane of the imidazole ring, whereas for ring B this is only 6.9° ; the methylamino group is almost in the same plane, and it is N-6 that carries the proton, and not N-3.⁸⁰ The dimethylamino group in **103**, which is essentially coplanar with the ring, clearly interacts more with N-1–C-5 than with the C-2–N-3 bond; an even larger interaction is apparent in the betaine **104**, even though the dimethylamino group is rotated out of the plane of the ring by about 12° .⁶²

2. MINDO/3 Calculations

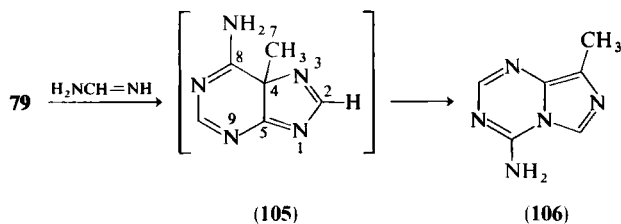
Reaction between **79** and formamidine (Scheme 25) gave not 5-methyladenine (**105**), but a rearranged product (**106**).⁶⁷ MINDO/3 calculations show that the two rings in **105** deviate considerably from coplanarity, with loss of conjugation and introduction of strain. Computed bond distances and

⁸⁰ H. Takayanagi, H. Ogura, K. Matsuzaki, K. Kitajima, and T. Nishimura, *Bull. Chem. Soc. Jpn.* **52**, 3358 (1979).

TABLE I
BOND DISTANCES (Å) AND ANGLES (°) FOR STRUCTURES **102**–**105**

Distances	By X-ray diffraction			By MINDO/3 105 ⁶⁷
	102 ⁸⁰	103 ⁵⁹	104 ⁶²	
N-1–C-2	1.432	1.407	1.487	1.41
N-1–C-5	1.279	1.305	1.342	1.30
C-2–N-3	1.309	1.281	1.266	1.30
N-3–C-4	1.473	1.469	1.488	1.47
C-4–C-5	1.519	1.526	1.527	1.57
C-2–X-6	1.335	1.517	1.696	—
C-4–X-7	1.419	1.534	1.513	1.56
C-4–C-8	1.530	1.525	1.531	1.56
C-5–X-9	1.463	1.345	1.329	1.37
Angles				
C-2–N-1–C-5	104.0	103.8	106.2	106.6
N-1–C-2–N-3	116.8	117.3	112.1	113.0
N-1–C-2–X-6	116.0	115.8	122.0	—
N-3–C-2–X-6	127.2	126.8	125.9	—
C-2–N-3–C-4	104.6	106.3	110.2	109.8
N-3–C-4–C-5	102.3	101.0	102.1	—
N-3–C-4–X-7	110.8	107.8	107.7	—
N-3–C-4–C-8	109.2	108.6	107.1	—
N-1–C-5–C-4	112.4	111.6	109.1	—
N-1–C-5–X-9	122.5	121.5	126.7	122.3
C-4–C-5–X-9	125.2	126.9	123.9	—

angles are included in Table I for comparison; of particular interest are the long C-4–C-5 and C-4–C-7 distances. Calculated heats of formation⁶⁷ of **105** and **106** were, respectively, 395 and 178 kJ/mol.



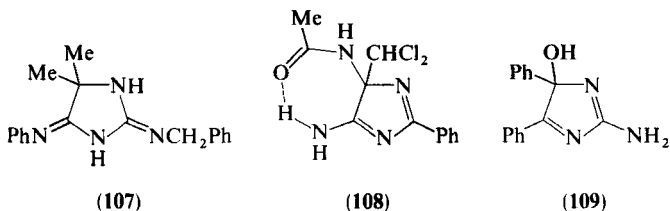
SCHEME 25

3. Tautomerism

a. *Ring–Ring.* Compound **88** is currently the only known example of a 4H-imidazole having a proton at C-4. MNDO calculations suggest that the CH tautomers of aminoimidazoles can be more stable than the NH forms.⁷²

b. *Ring-Chain*. 4,4-Disubstituted imidazoles formally bearing one or more C=O or C=S groups in the ring have been shown to exist exclusively as such, with no evidence of OH or SH tautomers⁸¹⁻⁸³; theoretical studies support these observations.⁸⁴

The situation is less clear with mono and diamino derivatives; examples of the latter have been claimed from IR evidence¹⁷ to exist in the exocyclic imino forms, e.g., **107**. Structure **39** is given as the product from Scheme 12 on the basis of three NH signals in the ¹H-NMR spectrum (Me₂SO-*d*₆),³⁶ but this could be accommodated by an intramolecular hydrogen bond as in **108**. Compounds **78**⁶⁶ and **79**⁶⁷ in the same solvent, for example, each show a two-proton singlet, indicating them both to be in the amino form. Spectroscopic data for the 2-amino compound **73** (IR, Nujol; ¹H-NMR, CDCl₃) have been interpreted in terms of a mixture of tautomers,⁶⁴ whereas for **109**, ¹H-NMR data (Me₂SO-*d*₆) suggest that the amino tautomer is present.³¹ In the solid state, **102** is in the amino form.⁸⁰



4. Dipole Moments

The dipole moment of the *N*-oxide **97** is reported as 5.8 D (benzene, 20°C).⁷⁹

B. SPECTROSCOPIC DATA

1. Ultraviolet Spectra

No simple tetraalkyl-4*H*-imidazoles have been reported, so UV spectra described are all modified by conjugation involving aryl or heteroatom substituents.

⁸¹ J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "Advances in Heterocyclic Chemistry," Suppl. 1, p. 373. Academic Press, New York, 1976.

⁸² J. T. Edward and I. Lantos, *J. Heterocycl. Chem.* **9**, 363 (1972).

⁸³ P. Sohar, J. Nyitrai, K. Zauer, and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **58**, 165 (1968) [*CA* **70**, 72310 (1969)].

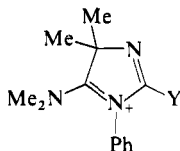
⁸⁴ A. Sayarh, M. Gelize-Duvigneau, J. Arriau, and A. Maquestiau, *Bull. Soc. Chim. Belg.* **88**, 289 (1979).

Structure **76** absorbs at 282 nm ($\log \epsilon$ 3.99),⁶⁵ whereas 4-hydroperoxy-triaryl compounds (e.g., **43**) show two peaks, respectively, in the ranges 225–230 and 280–307 nm^{40,41,44}; both latter peaks are of similar intensity ($\log \epsilon \sim 4.20$) and the second is sensitive to the aryl substituent. The effect of the 2-substituent on the spectra of, for example, **54** and **84** has also been discussed.^{84a}

Bis(methylmercapto) compound **7** shows λ_{\max} at 257 nm ($\log \epsilon$ 3.83)⁷ and the related 4,4-dibenzyl compound at 261 nm (4.12).¹¹

5-Amino-substituted compounds show a peak in the range 267–275 nm ($\log \epsilon$ 3.76–3.99),^{58,59,67} whereas an additional 2-aryl substituent results in two maxima [228–241 nm ($\log \epsilon$ 3.95–4.25) and 276–289 nm ($\log \epsilon$ 3.60–4.04)].⁵⁷ 2-Amino-5-aryl compounds (e.g., **34**) have had only one peak described: 273–278 nm ($\log \epsilon$ 3.6–3.85)^{26,29}; its position was taken as evidence that the phenyl group was conjugated and not at C-4.²⁶

The dipolar ion **110** has three regions of absorption (230, 259, and 298 nm), whereas its *S*-methyl derivative **111** has but one: 242 nm ($\log \epsilon$ 4.39).⁶¹ Unstable *N*-oxide **97** has λ_{\max} 241.2 nm ($\log \epsilon$ 4.05)⁷⁹; whereas **94** and **96** both absorb at 360 nm,⁶⁵ **95** absorbs at 324 nm.⁷⁷



(110) Y = S⁻

(111) Y = SMe

2. Infrared Spectra

4*H*-Imidazoles appear to have two bands in their IR spectra arising from the unsaturated part of the ring, but the frequencies are sensitive to the nature of the ring substituents.^{16,19,29,35,58,83,85,86} In structures **21**, having R¹–R³ = alkyl, these were assigned “Imidazole I” (1613–1621 cm⁻¹) and “Imidazole II” (1511 cm⁻¹); a ring mode was identified between 948 and 963 cm⁻¹.⁸⁵ In **4**, the bands were found at lower frequency (1555 and 1940 cm⁻¹) and peaks at 1195, 1170, and 1105 cm⁻¹ were assigned to the thiolimidate moiety.⁸³ The presence of a 2-dialkylamino and a 5-phenyl group (e.g., **34**) causes a high-frequency shift,²⁹ ranges being 1650–1625 and 1575–1567

^{84a} Y. Sakaino and H. Kakisawa, *Nippon Kagaku Kaishi*, 1449 (1978) [CA **90**, 38188 (1979)].

⁸⁵ P. Bassignana, C. Cogrossi, M. Gandino, and P. Merli, *Spectrochim. Acta* **21**, 605 (1965).

⁸⁶ I. K. Korobeinicheva, M. M. Mitsov, V. S. Kobrin, and L. B. Volodarskii, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 96 (1976) [CA **85**, 26913 (1976)].

cm^{-1} ; for 5-dialkylamino derivatives only one peak (between 1600 and 1580 cm^{-1} , usually close to 1595 cm^{-1}) has been recorded^{57,59,72} (but see Ref. 58). Frequencies as high as 1680–1670 cm^{-1} have been taken as evidence for exocyclic imino groups (e.g., **107**).^{17,64,66}

In other examples, only one peak is reported, possibly because of difficulties in distinguishing from aryl absorptions^{44,47,48}; IR spectral differences among the three isomeric tetraphenylimidazoles have been discussed.³⁵

Salt **111**, and its \dot{N} -*i*Pr analog, have peaks, respectively, at 1670 and 1623⁶¹ and at 1660 and 1600 cm^{-1} .⁶² Spectra have been reported for dipolar ions **68**^{61,62} and **71**.⁶³

A comparative spectral study (IR and laser Raman) among 4*H*-imidazoles and their 1- and 3-oxides and their 1,3-dioxides showed that a band assigned to a $\nu_{\text{C}=\text{N}}$ out-of-plane vibration was very sensitive to the position of the *N*-oxide group.⁸⁶

A band between 2860 and 2810 cm^{-1} (intramolecular H bond)^{40,41,44} and one near 850 cm^{-1} ($\nu_{\text{O}-\text{O}}$)⁴⁴ were used in structure confirmation of, e.g., **43** and **47**.

3. ¹H-Nuclear Magnetic Resonance Spectra

The ¹H-NMR signal for the proton at C-4 in **88** (Scheme 26), the only 4*H*-imidazole known to be stable in this tautomeric form, is found at δ 5.17.⁷² Only single examples of a base (**79**)⁶⁷ and a cation (**74**)⁶⁴ with a proton at C-2 have had spectra recorded (Scheme 26); no data are available for protons at C-5.

Methyl groups at C-2 give signals near δ 2.50,⁴⁷ δ 2.35^{47,48,65} (e.g., **76**), or 2.16⁵⁹ (e.g., **114**), depending on ring substituents. Both single and geminal methyl groups at C-4 absorb in the range δ 1.43–1.63^{26,29,48,57–59,64,65,67} (Scheme 26), exceptions being dipolar ions^{61–63} (e.g., **110**) and cations^{61,62} (e.g., **111**). Data for methyl groups at C-5 are lacking.

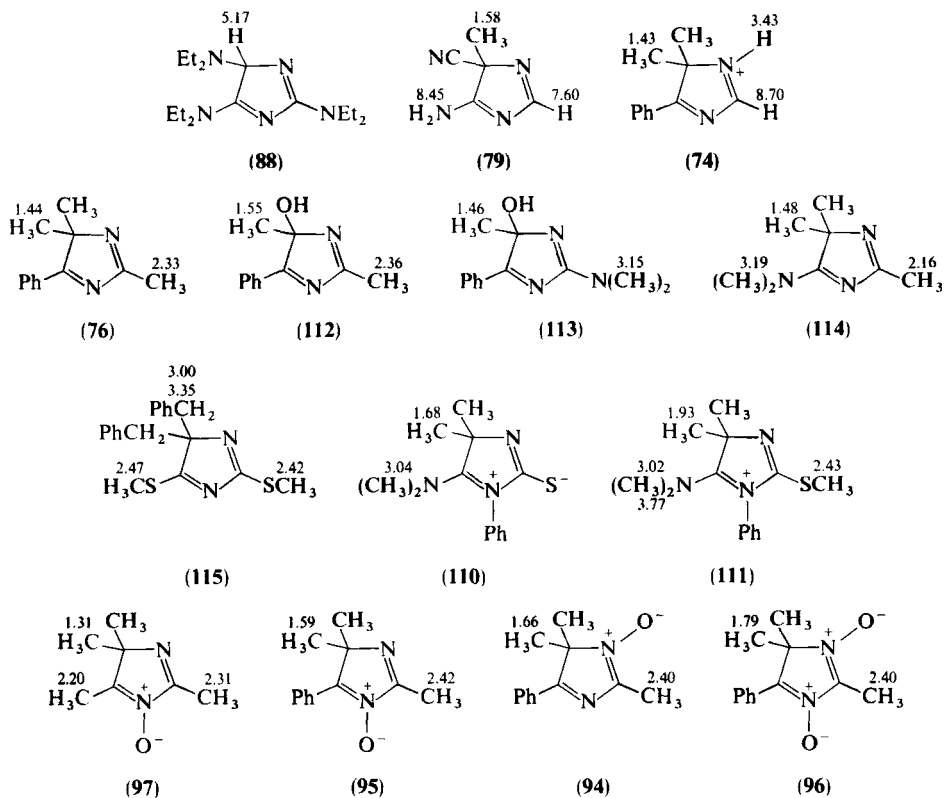
Dimethylamino groups, both at C-2^{29,31} and C-5,^{57–59} give signals between δ 3.10 and 3.26; methylmercapto groups fall likewise in a narrow range (δ 2.42–2.70).^{11,87}

4-Hydroxy groups absorb in the range δ 3.6–6.1, depending on the solvent,^{26,29,31,80} whereas 4-hydroperoxy proton signals come between δ 11.95 and 14.40.^{40,41,47}

The benzyl methylene groups in **115** are diastereotopic ($J = 13.5$ Hz)¹¹; restricted rotation of the dimethylamino group is apparent in **111**.⁶¹

Data (CD_3OD) for some *N*-oxides (**94**–**97**) are also illustrated.^{65,77}

⁸⁷ P. Sohar, J. Nyitrai, K. Zauer, and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **65**, 189 (1970) [*CA* **73**, 104026 (1970)].



SCHEME 26

4. ^{13}C -Nuclear Magnetic Resonance Spectra

All recorded spectra have been for samples having NR_2 at C-5, the signal for this ring carbon atom falling in the range δ 179.6–188.9^{57–59,67,71,72}; the NMe_2 carbons absorb between δ 38.6 and 39.6.^{57–59} Most examples, in addition, have a geminal dimethyl group at C-4, the ring carbon absorbing in the range δ 73.2–74.2,^{57–59} and the methyl groups between δ 22.1 and 23.7.^{57–59,67} Other substituents at C-4 have resulted in a signal range of δ 66.4–115.9.^{67,71,72} A wide variety of substituents at C-2 results in a chemical shift range δ 162.7–180.7.

^{13}C -NMR spectroscopy has been used to distinguish the isomeric triarylimidazolyl dimers.⁸⁸

⁸⁸ G. Domany, J. Nyitrai, K. Lempert, W. Voelter, and H. Horn, *Chem. Ber.* **111**, 1464 (1978).

5. Mass Spectra

Most recorded mass spectra show a parent ion (1–30%).^{26,29,31,57–59,61,67,89,90} The major fragmentation process, as with 2*H*-imidazoles,¹ is loss of RCN, which can and frequently does occur in two different ways; this often leads to the base peak. Loss of a 4-substituent to give a delocalized cation can also compete as the primary process^{26,29,57,90}

The fragmentation pattern of **4** has been studied in detail, using deuterium labeling.⁸⁹ The patterns for **37** and its 2*H* analog are essentially the same, though quite different from that of 1,2,4,5-tetraphenyl-1*H*-imidazole.⁹⁰

IV. Reactions of 4*H*-Imidazoles

A. THERMAL REACTIONS FORMALLY INVOLVING NO OTHER SPECIES

Rearrangements of the van Alphen–Hüttel type, involving migrations of carbon-linked substituents around the ring, and characteristic of the 2*H*- and 3*H*-pyrroles,⁹¹ the 3*H*- and 4*H*-pyrazoles,² and the 2*H*-imidazoles,¹ are rare among 4*H*-imidazoles because of lack of suitably substituted examples. A number of other thermal reactions are known, including the extensively studied rearrangements of structure types **2** and **21**.

1. Isomerizations

a. *Two Carbon Substituents at C-4*. At 300°C, but not under electron impact, **37** rearranges quantitatively to 1,2,4,5-tetraphenyl-1*H*-imidazole.⁹⁰ The conversion of the transiently formed 5-methyladenine (**105**, Scheme 25) to **106** involves ring opening and not methyl migration⁶⁷; the same is apparently true for transient 5-substituted guanines.⁹²

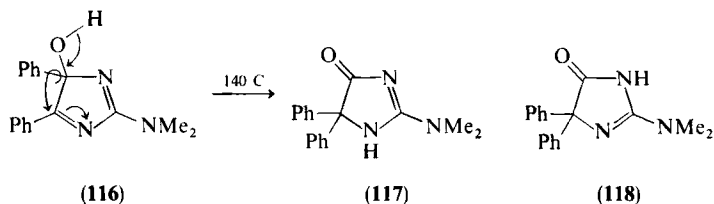
b. *Hydroxy Group at C-4*. When a 4-aryl substituent is also present, a benzil–benzilic acid type rearrangement occurs, both thermally^{31,42,52} and under base catalysis.^{23,30,31} For the example in Scheme 27, **116** is converted to **117** ($\nu_{\text{C=O}}$ 1680 cm⁻¹), which exists as such and not as **118**.³¹ Lempert and co-workers isolated an analog of **117** directly from the base-catalyzed

⁸⁹ K. Lempert, K. Zauer, J. Moeller, and G. Schroll, *Acta Chem. Scand.* **26**, 1542 (1972).

⁹⁰ G. Domany and J. Nyitrai, *Acta Chim. Acad. Sci. Hung.* **90**, 109 (1976) [*CA* **86**, 72522 (1977)].

⁹¹ M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.* **32**, 234 (1982).

⁹² J. B. Holtwick and N. J. Leonard, *J. Org. Chem.* **46**, 3681 (1981).

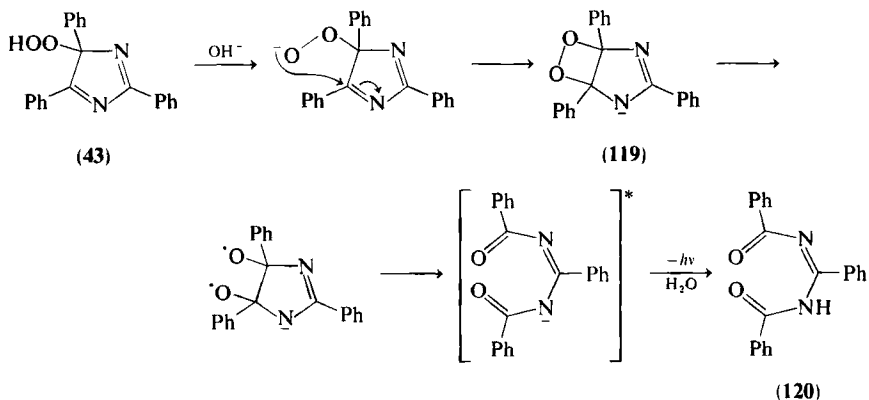


SCHEME 27

reaction between benzil and guanidine.⁹³ Cyclohexanedione has been proposed to undergo ring contraction prior to imidazole-ring formation.⁹⁴

When a 4-methyl group is present, the reaction follows a different course (Section IV,D,1,c); earlier claims of an acid-catalyzed rearrangement to the isomeric 4-hydroxymethyl-1*H*-imidazole^{26,28} were later corrected.²⁹

c. *Hydroperoxy Group at C-4.* The chemiluminescence of lophine (42) in the presence of air and base was referred to earlier³⁹; hydroperoxide 43 also emits light of the same frequency, both thermally and on base treatment,^{40,41} showing it to be an intermediate in the chemiluminescent reaction. The mechanism appears to be as in Scheme 28^{40,41,44}; a nonanionic dioxetane related to 119 has been isolated and converted thermally to the analogous 120.⁹⁵ A radical mechanism for the thermal process has also been suggested.⁴⁷



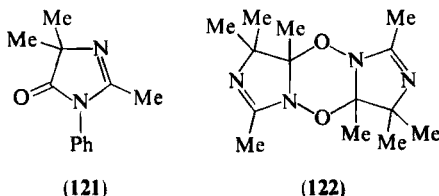
SCHEME 28

⁹³ M. Lempert-Sréter, V. Solt, and K. Lempert, *Magy. Kem. Foly.* **69**, 237 (1963) [*CA* **59**, 10022 (1963)].

⁹⁴ M. Furukawa, T. Yoshida, and S. Hayashi, *Chem. Pharm. Bull.* **23**, 580 (1975).

⁹⁵ G. Rio and B. Serkiz, *J. C. S. Chem. Commun.*, 849 (1975).

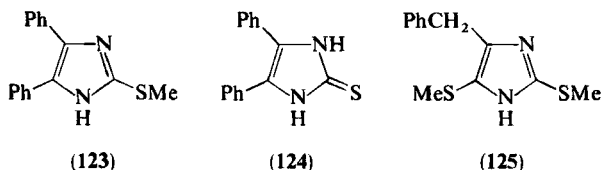
d. *N-Oxides*. Thermolysis of **95** in benzene yields **121**⁹⁶; in contrast, the 5-methyl analog **97** dimerizes spontaneously to **122**.⁷⁹



2. Migration of 4-Aryl Group with Loss of S-Alkyl Group

Structures **2** and **21** can be rearranged under aluminum chloride catalysis, on thermolysis in various solvents, or on dry heating.

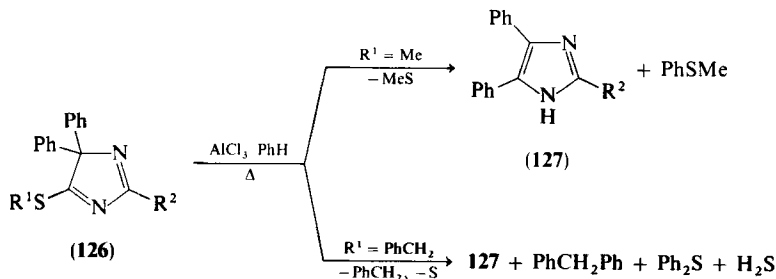
a. *Aluminum Chloride Catalysis*. Treatment of **4**, **9**, and **10** in refluxing methylbenzene with aluminum chloride results in loss of the 5-alkylmercapto group and migration of phenyl to this position by what is believed to be a cationic mechanism.¹² Whereas **4** and **10** both yield **123**, **9** gives **124** from S-debenzylation.¹² S-Debenzylation of **10** to the two desmotropic forms of **6** had been observed in the lower boiling benzene⁸; also **9**, on a short period of boiling in this solvent, yields **5**.⁹⁷ Structure **115** is anomalously C-debenzylated in benzene to give **125** and diphenylmethane.¹¹



For **126** ($R^2 = \text{Me}, \text{PhCH}_2$) rearrangement gives the corresponding **127** (Scheme 29), but the by-products depend on the nature of R^1 .¹⁹ An SMe group is lost intact, producing methylmercaptobenzene with the solvent; for $R^1 = \text{PhCH}_2$, the benzyl group is lost first, giving diphenylmethane, the sulfur leaving subsequently and producing initially thiophenol and then diphenyl sulfide with hydrogen sulfide from disproportionation.

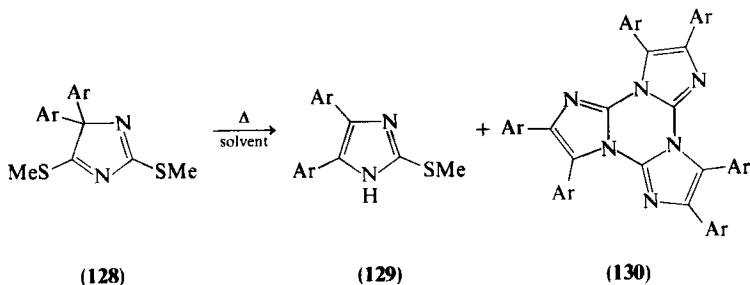
⁹⁶ L. B. Volodarskii and V. S. Kobrin, *Khim. Geterotsikl. Soedin.*, 1423 (1976) [*CA* **86**, 55349 (1977)].

⁹⁷ G. Domany, J. Nyitrai, K. Zauer, K. Lempert, and S. Békassy, *Acta Chim. Acad. Sci. Hung.* **80**, 101 (1974) [*CA* **80**, 95826 (1974)].



SCHEME 29

b. *Thermolyses with or without Solvent.* During a study into methylation-demethylation reactions of **4**, using trimethylanilinium ethoxide at 180°C, **123** was isolated. It was subsequently obtained in high yield together with 4-methylmercapto-*N,N*-dimethylaniline on heating **4** with *N,N*-dimethylaniline at 180°C.⁹⁸ It was further shown that in various solvents between 145 and 215°C, **128** (Scheme 30) rearranged to a mixture of **129** and the triazole trimer **130**⁹⁹; the latter was favored by temperatures higher than the melting point of **128**, whereas in methylbenzene or methoxybenzene **129** was the major product. Direct thermolysis (240°C) of **4** gave a high yield of **130** together with dimethyl disulfide; in contrast, a mixture of **124** (53%) and **130** (22%) was formed from **10** at 200°C.⁹⁹



SCHEME 30

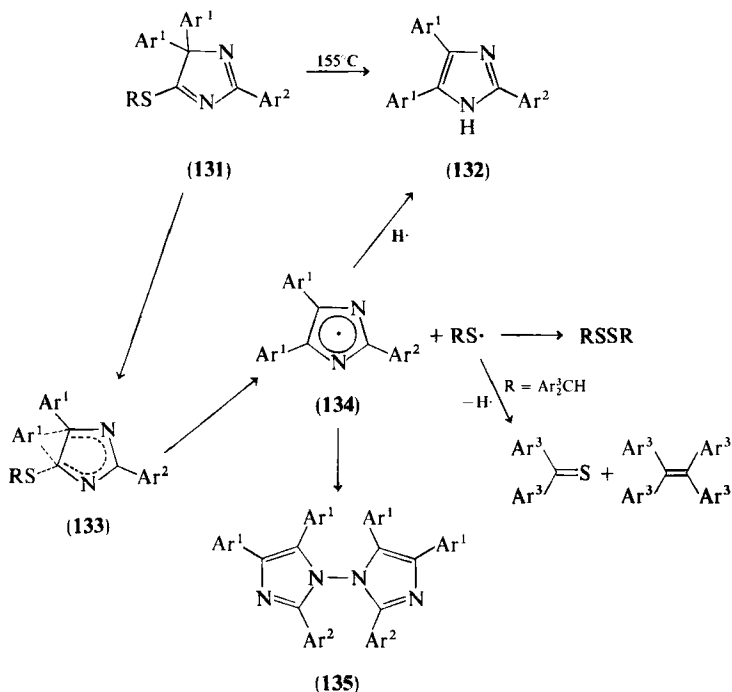
The rearrangement of compounds **131** to **132** in a number of solvents at 155°C has been shown to proceed via a free radical process (Scheme 31).^{100,101} The reaction is first order, little affected by solvent, and there is

⁹⁸ K. Zauer, I. Zauer-Csullog, A. Hevér, and K. Lempert, *Magy. Kem. Foly.* **76**, 365 (1970) [*CA* **73**, 87847 (1970)].

⁹⁹ K. Zauer, I. Zauer-Csullog, and K. Lempert, *Chem. Ber.* **106**, 1628 (1973).

¹⁰⁰ J. Nyitrai and K. Lempert, *Chem. Ber.* **107**, 1637 (1974).

¹⁰¹ J. Nyitrai, K. Lempert, and T. Cserfalvi, *Chem. Ber.* **107**, 1645 (1974).



SCHEME 31

no correlation between the rate and the Ar^1 para-substituent σ^+ constant.¹⁰¹ For $\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$, $\Delta H^\ddagger = 106 \text{ kJ/mol}$ and $\Delta S^\ddagger = -75 \pm 3 \text{ J/mol/K}$; because the C—S bond energy must be close to 250 kJ/mol, a concerted process is indicated via **133**.¹⁰¹ Crossing experiments have confirmed an intramolecular rearrangement.¹⁰² The intermediacy of **134** was strongly implied by the isolation of **135** ($\text{Ar}^1 = \text{Ar}^2 = 4\text{-ClC}_6\text{H}_4$) from thermolysis of the corresponding **131** ($\text{R} = \text{Me}$)⁸⁸; formation of $\text{RS}\cdot$ radicals is apparent from a variety of products from further reaction (Scheme 31).¹⁰⁰

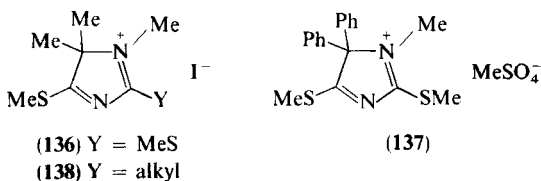
B. REACTIONS OF RING ATOMS WITH ELECTROPHILES

1. Salt Formation

a. *Protiosalts*. Structure **74** is one of the only examples of protiosalts to have been described⁶⁴; in most cases the 4*H*-imidazole ring system is either destroyed in aqueous acid^{49,67} or undergoes subsequent addition (Section IV.B,2).

¹⁰² E. Koltai, J. Nyitrai, K. Lempert, and L. Bursics, *Chem. Ber.* **107**, 1649 (1974).

b. *Methosalts*. Compound **11** ($\text{NR}_2 = \text{morpholino}$) gives a dimethiodide, but no structure has been suggested.¹⁴ Alkylation of structures **2** with methyl iodide or methyl *p*-toluenesulfonate takes place at N-3 and not at N-1 to give, e.g., **136**,⁹ a result confirmed later by the conversion of **4** to **137**, using dimethyl sulfate.^{103,104} Ethosalts have also been prepared, using ethyl *p*-toluenesulfonate.⁹ Methyl iodide in ether gives **138** ($\text{R} = \text{Me}, \text{Et}$) with the appropriate **21**, alkylation again occurring at N-3.¹⁸

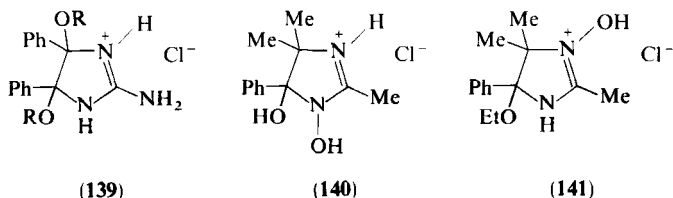


Methylation of dipolar ions **68** occurs exclusively at sulfur to yield, e.g., **111**^{61,62}; the N-analogs **71** give a mixture of products from methylation at both the exo- and the endocyclic nitrogen atoms.⁶³

2. Protonation Followed by Addition

Treatment of **109** with concentrated hydrochloric acid converts it to the hydrochloride salt **139** ($\text{R} = \text{H}$), presumably via protonation and covalent hydration³¹; related compounds had been reported earlier.^{22,23} In the presence of methanol, **139** ($\text{R} = \text{Me}$) is the product.³¹

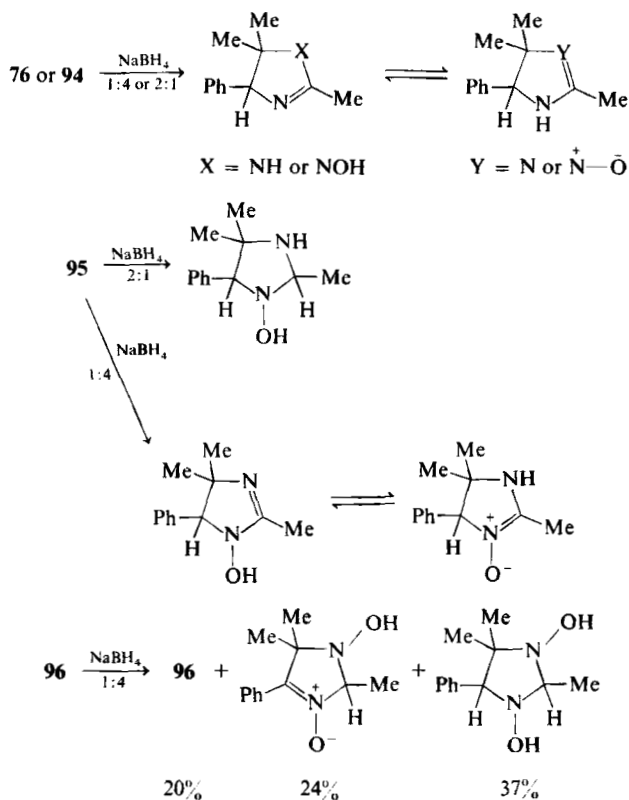
Passage of hydrogen chloride into ether solutions of **76** and *N*-oxides **94**–**97**^{65,79} results similarly in protonation and hydration. Thus, for example, **95** gives **140**, convertible back to **95** with base; likewise, among other examples, **94** is converted to **141** in ethanol.⁶⁵



In strong hydrochloric acid, **51** is cleaved to benzil and benzamidine, perhaps via an analogous covalent hydrate⁴⁹; ethanoic acid similarly cleaves **44**.⁴²

¹⁰³ K. Lempert and K. Zauer, *Tetrahedron Lett.*, 519 (1964).

¹⁰⁴ K. Lempert and K. Zauer, *Acta Chim. Acad. Sci. Hung.* **47**, 391 (1966) [*CA* **65**, 8893 (1966)].



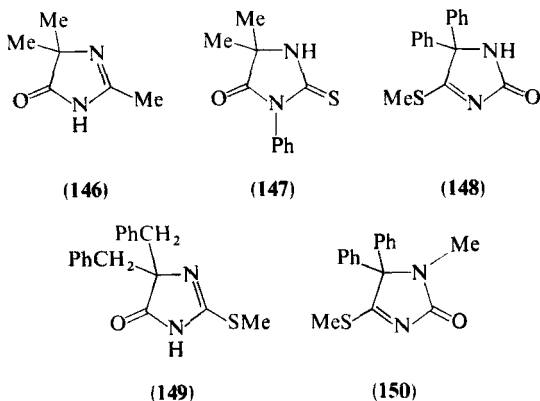
SCHEME 33

2. Displacement of Ring Substituents

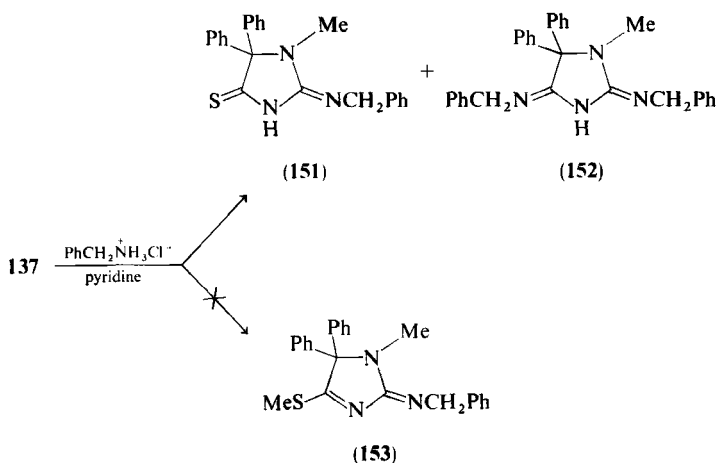
The groups NR_2 , OR, SR, and Cl have been displaced by a number of nucleophiles.

a. *With Formation of a Carbonyl Group.* Aqueous or methanolic hydrogen chloride readily hydrolyzes dimethylamino groups^{57,59}—**114**, for example, giving **146**⁵⁹; dipolar ions **68** and **71** are hydrolyzed in water^{61–63}—**147**, for example, being the product from **110**.⁶¹

Structures **16**,¹⁶ **2** ($\text{R}^1\text{—R}^4 = \text{Me}$),¹⁰ **4**, **7**,⁷ and **137**,^{103,104} are all converted to the corresponding hydantoin by aqueous or methanolic hydrochloric acid, but it is possible to achieve selective hydrolysis. Thus, with aqueous ethanoic acid, **4** yields **148** (64%),⁷ whereas methanolic chloroethanoic acid cleaves **115** to **149** (86%)¹¹; the salt **137** gives **150** in aqueous methanol.^{103,104}



b. *With Formation of an Exocyclic Imine.* The *S*-methyl group in both iodide salts in Scheme 6 is displaced by reaction with primary amines to give the same diimine, one being formed via a Dimroth rearrangement. Thus when $R = \text{Ph}$, phenylmethanamine gives **107**.¹⁷ Conversion of **137** to **151** together with a small amount of **152** (Scheme 34) is believed to proceed via aminolysis of one *S*-methyl group, followed by *S*-demethylation by pyridine.¹⁰⁶ The main product was shown not to be **153**, as had been reported earlier.¹⁰⁴

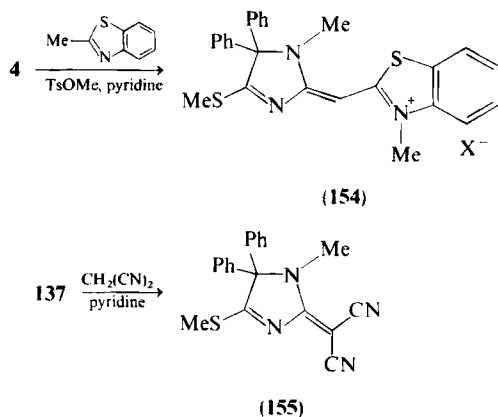


SCHEME 34

¹⁰⁶ K. Lempert, P. Sohar, and K. Zauer, *Acta Chim. Acad. Sci. Hung.* **63**, 87 (1970) [*CA* **72**, 55333 (1970)].

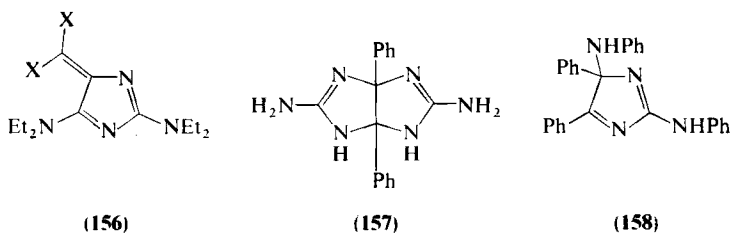
c. *With Formation of an Exocyclic C=C Bond.* A wide range of cyanine dyes has been prepared by treating a mixture of **2** and a heterocycle having an acidic methyl group with excess of a methylating agent and base. Thus **4** with 2-methylbenzothiazole is converted via **137** to **154** (Scheme 35).⁹ Malononitrile in pyridine likewise gives **155** (85%),¹⁰³ but similar products are not formed with other acidic methylene compounds.

Treatment of **87** with CH_2X_2 ($\text{X} = \text{COMe}, \text{CN}, \text{CO}_2\text{Et}$) in boiling benzene gives the corresponding **156**.⁷¹



SCHEME 35

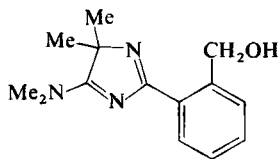
d. *Other Reactions.* In dry tetrahydrofuran, **109** is converted to **157**; the same product is formed from benzil and guanidine in dioxane or methanol.^{31,93} The 4-chloro group in structures **41** may be displaced both by aromatic amines and by ethanol.³⁷ When $\text{R}^2 = \text{Cl}$, both chlorines are displaced,³⁷ aniline giving, for example, the preemergence herbicide **158**.³⁸



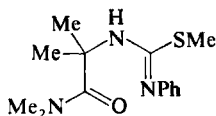
3. Ring Opening

A mixture of phthalide and *o*-(hydroxymethyl)benzoic acid is formed from **159** and 1 *M* sodium hydroxide.⁵⁷ The dipolar ion **111** is cleaved to **160** by

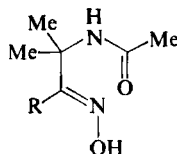
aqueous potassium carbonate.⁶¹ *N*-Oxide **95** is opened to the amido oxime **161** (*R* = Ph) by sodium hydroxide⁷⁷; **97** is cleaved similarly, even by water.⁷⁹



(159)



(160)

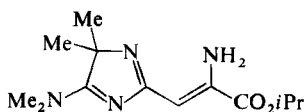


(161)

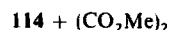
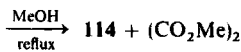
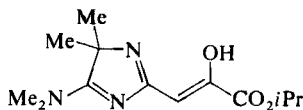
D. REACTIONS OF RING SUBSTITUENTS

1. *C*-Linked

a. *Substituent at C-2*. The alcohol **159** is readily acetylated at oxygen with ethanoic anhydride and pyridine.⁵⁷ Structure **162** is fragmented to **114** in two stages (Scheme 36).⁵⁹



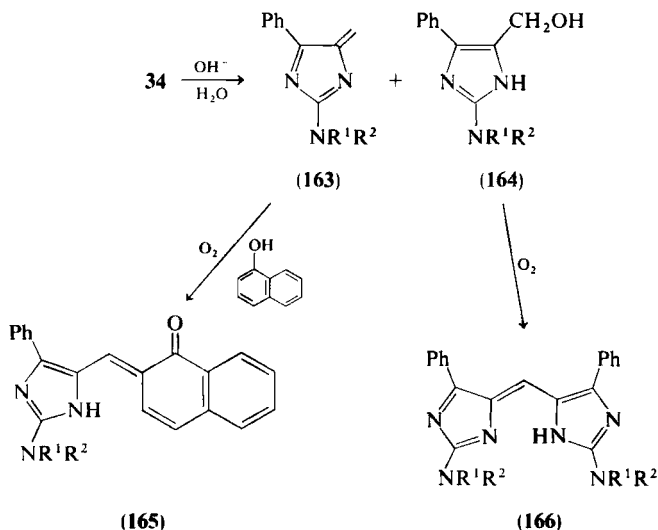
(162)



SCHEME 36

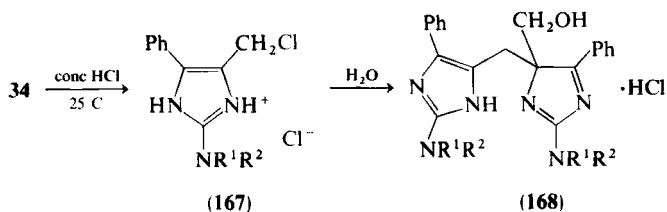
b. *Nitrile Group at C-4*. Formation of **106** (Scheme 25) from **79** is by attack of the amidine at the nitrile group.⁶⁷ Hydrolysis of **93** (10% sulfuric acid) leads via decarboxylation to **42**.⁷⁵

c. *Methyl and Hydroxyl Groups at C-4*. During studies^{26,27} into the mechanism of the Voges–Proskauer reaction,^{24,25} it was concluded that under the prevailing basic, oxidizing conditions, the initially formed **34** was dehydrated (to **163**) and rehydrated (to **164**) in the process of forming the observed violet pigments **165** and **166** (Scheme 37).



SCHEME 37

Hydrochloric acid converts **34** to **167** presumably via **163** (Scheme 38), which on subsequent treatment with water yields **168** together with the salt of **164**.²⁹ This work corrected earlier reports.^{26,28}



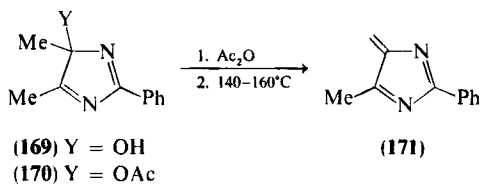
SCHEME 38

2. *N*-Linked

Structure **78** is acylated (80%) on the exocyclic nitrogen atom with ethanoic anhydride.⁶⁶

3. *O*-Linked

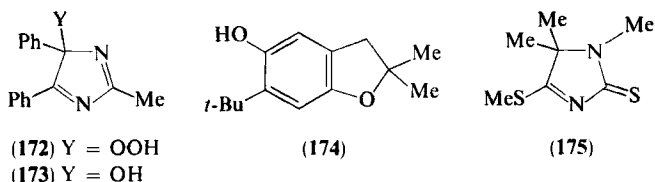
The hydrochloride **169** (Scheme 39) is claimed to give the acyl derivative **170**, which on pyrolysis yields **171**.²² It is possible, in view of the work of



SCHEME 39

Nishimura *et al.*,²⁹ that **169** may have the isomeric hydroxymethyl 1*H*-imidazole structure.

Hydroperoxide **172** is reduced to **173** by triphenylphosphine.⁴⁴ 2,5-Di-*tert*-butyl-1,3-benzoquinone is isomerized to **174** by boiling with **43** in methylbenzene; isomerizations of this type normally must be induced photochemically.¹⁰⁷



4. *S*-Linked

Reactions involving sulfur-linked substituents have been exclusively de-alkylations of *S*-alkyl substituents to yield a thiocarbonyl group. Debenzylations under mild conditions with aluminum chloride in benzene were mentioned earlier (Section IV,A,2,a).^{8,97} Pyridine demethylates salts **137** selectively to give **175**.¹⁰³

¹⁰⁷ E. F. Ullman, U.S. Patent 3,689,391 (1972) [CA **78**, 3585 (1973)].

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